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A DANISH POPULATION-BASED STUDY

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BY
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AALBORG UNIVERSITY
DENMARK

OCCUPATIONAL EXPOSURE AND COPD

A DANISH POPULATION-BASED STUDY

PhD thesis

Else Toft Würtz

AALBORG UNIVERSITY
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ORIGINAL PAPERS

The thesis is based on the following original research papers:

Paper I   Occupational chronic obstructive pulmonary disease in a Danish population-based study

Accepted paper:
Würtz et al. COPD. 2014 Nov 21. [Epub ahead of print]

Paper II   Occupational chronic obstructive pulmonary disease among Danish women: a population-based cross-sectional study

Submitted manuscript

Paper III   Occupational COPD among Danish never smokers – a population-based study

Accepted paper:
Würtz et al. Occup Environ Med. 2015 Jun;72(6):456-9

Paper IV   Occupational exposure increases the four-year incidence of COPD among 45-84-year old Danes

Submitted manuscript

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PREFACE

My engagement in occupational COPD was initiated by Øyvind Omland. I submitted an application as research assistant in his review project regarding occupational COPD. I was late for the job interview, but he luckily believed in my skills as a Master of Health Science. I think I caught up well on the untimely start and have thus ended up writing this thesis. With a prior career as biomedical laboratory scientist in cytology this was not straight forward, but thank you Øyvind, that you believed in me and have supported me all the way – although I am not a physician! I have learned a lot and I appreciate working within the field of medical research.

The last three years have been a long journey with many different tasks in relation to the PhD assignment. I have a lot of people I wish to thank for their help, understanding and support during the process:

- My co-supervisors Tine Halsen Malling for giving a wonderful daily support and always being understanding, Vivi Schlünssen for giving great methodological response and encouragement, Jens Georg Hansen for having great knowledge and facts about the data set, and Charlotte Brasch-Andersen being essential for the ongoing genetic part of my study.
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Else Toft Würtz

ENGLISH SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is a common disease affecting morbidity, disability and mortality all over the world and is characterised by airflow limitation due to the chronic inflammation. In populations aged above 40 the prevalence is about 10% and higher among men than among women. The main risk factor for COPD is smoking, although only a fraction of approximately 25% of continues smokers develop COPD. Nevertheless, about 80% of COPD cases could be attributed smoking.

Among other risk factors are occupational exposures in which vapour, gas, dust, and/or fume (VGDF) can induce chronic inflammation similar to effects seen from particles inhaled by smoking. The population attributable fractions (PAF) of occupational COPD are about 15% of the COPD cases.

The thesis aim to address the association between COPD and occupational exposure in a population-based cohort of Danes aged 45-84-years (Paper I-IV).

The population included 1626 women and 3091 men (N=4717) and baseline data were assessed in 2004/2006 while follow-up data (N=2624) were assessed in 2008/2010 and each time recruited through their general practitioner. Data were based on lung function measurements and questionnaires. COPD was defined by lung function measurements according to the method of Lower Limit of Normal (LLN).

A priori the Danish version of the International Standard Classification of Occupations, revision 1988 (DISCO-88) were used to select jobs with known presence of occupational exposure. The self-reported jobs with occupational exposure were then restricted to those included among the selected DISCO-88 codes. The cumulated occupational exposure was expressed as duration of exposed jobs. The main occupational exposure was organic dust (primarily agriculture) while 49% reported no lifetime occupational exposure.

Paper I included the whole baseline study population with 279 COPD cases and found an age-standardised prevalence of COPD at 5.0% (95% CI: 5.0;5.0) significant lower in women compared to men, 4.6% (95% CI: 4.6;4.6) and 5.0% (95% CI: 5.0;5.0), respectively. The adjusted odds ratio (ORadj) from the mixed model regression analysis, for medium (5-14 years) VGDF exposure was 1.61 (95% CI: 1.03;2.51), while the ORajd for high (≥15 years) organic dust exposure was 1.56 (95% CI: 1.09;2.24). Significant trends in exposure level were also present in these associations, p=0.031 and p=0.017, respectively.

Paper II included the women (N=1626) from the baseline study population. In all 279 women were assigned a relevant occupational exposure while 76 had COPD. The occupational exposures were dichotomised as never or ever occupational exposed. The mixed model regression analyses revealed occupational exposure to be asscociated to COPD, ORadj if exposed to VGDF and organic dust, 1.98 (95% CI: 1.06;3.69) and 2.05 (95% CI: 1.04;4.08), respectively. The PAF were estimated to be 14% and 15%, respectively.

Paper III included the never smokers (N=1575) from the baseline study population. Occupational exposure were present in 658 (42%) of the never smokers and 26 had COPD equal to a prevalence of 1.7%. The occupational exposures were dichotomised as never or ever occupational exposed. In the mixed regression model never smokers exposed to VGDF and organic dust had an increased occurrence of COPD, ORadj 3.69 (95% CI: 1.36;10.04) and 2.94 (95% CI: 1.05;8.22), respectively. The study PAF for COPD among never smokers caused by occupational exposure was 48% (95% CI: 30;65) for VGDF exposure and 41% (95% CI: 19;62) for organic dust exposure.

Paper IV was focusing on COPD incidence and annual decline in lung function in the four-year follow-up study. COPD cases at baseline were excluded (n=120) thus 2624 very eligible for analysis. The overall annual mean (±SD) change in lung function in men was ΔFEV_1 -50 mL/yr (±94) and ΔFVC -58 mL/yr (±133) and in women -31 mL/yr (±69) and -38 mL/yr (±105), respectively. No analyses of annual decline in lung function in relation to occupational exposures reach statistical significance. New-onset COPD was identified in 38 subjects and the age-standardised incidence was 0.9% (95% CI: 0.9;0.9) (men 1.0% (95% CI: 1.0;1.0), women 0.7% (95% CI: 0.7;0.7)). The adjusted incidence rate ratios (IRR) from the mixed regression analyses on occupational exposures were associated with COPD; low (<5 years) VGDF exposure 3.71 (95% CI: 1.17;11.8), high VGDF exposure 2.62 (95% CI: 1.06;6.48), low organic dust exposure 3.24 (95% CI: 1.07;9.83), but with no clear exposure-response relation.

The results from this thesis suggest occupational exposures to be associated to COPD. COPD was associated to occupational exposure also in never smokers and women. We found exposure-response relation in the cross sectional analyses, but not supported in the longitudinal analyses. The VGDF exposure consisted predominantly of organic dust. The results are in accordance with other international studies. However, the estimated PAFs were higher among never smokers compared to earlier studies, while to our knowledge, no comparable PAF previously have been established among women. The longitudinal analyses indicate an association between occupational exposure and incident COPD despite the short follow-up time.

The present study emphasise the major influence that exposures from occupation as VGDF and organic dust have on COPD, also among never smokers and women. These findings from the labour market in Denmark might indicate that even low exposures from work over time can have an impact on the development of COPD. The awareness by recognising these data ought to be transformed to preventive efforts to eliminate occupational COPD and thus improve public health.

DANSK RESUMÉ

Kronisk Obstruktiv Lungesygdom (KOL) er en udbredt sygdom der påvirker morbiditet, invaliditeten og mortaliteten over hele verden. KOL er karakteriseret ved en nedsat lungefunktion på grund af en kronisk inflammation i lungerne. Prævalensen er ca. 10 % hos befolkningen over 40 år, og er højere blandt mænd end blandt kvinder. Den væsentligste risikofaktor for KOL er rygning, selvom kun ca. 25 % af rygere får KOL. Alligevel kan rygning kun forklare optil ca. 80 % af KOL tilfældene.

En anden risikofaktor er erhvervsmæssig eksponering for damp, gas, støv og/eller røg (VGDF) der ved KOL foranlediger en kronisk inflammation med tilsvarende effekt som partiklerne der inhaleres ved rygning. Den andel af KOL der kan undgås hvis den erhvervsmæssige eksponering fjernes er ca. 15 % (the population attributable fraction (PAF)).

Formålet med denne afhandling er at se på associationer mellem KOL og erhvervsmæssige eksponeringer i en kohorte af den danske befolkning i alderen 45-84 år (Artikel I-IV).

Baseline data blev indsamlet i 2004/2006 og kohorten inkluderede 1626 kvinder og 3091 mænd (N=4717), mens de longitudinelle data (N=2624) blev indsamlet i 2008/2010, begge gange via deres egen praktiserende læge. Data var baseret på lungefunktionsmålinger og spørgeskemaer. KOL blev defineret ud fra lungefunktionsmålingerne og den nedre normale referencegrænse (Lower Limit of Normal (LLN)).

A priori blev der udvalgt job koder med kendt erhvervsmæssige eksponeringer ud fra den danske version af 'The International Standard Classification of Occupations, revision 1988' (DISCO-88). De selvrapporterede job med en erhvervsmæssig eksponering blev efterfølgende afgrænset til de a priori udvalgte DISCO-88 koder. Den mest udbredte erhvervsmæssige eksponering var organisk støv (primært landbrug) mens 49 % ikke rapporterede nogen form for erhvervsmæssig eksponering i deres arbejdsliv.

Artikel I inkluderede hele baseline kohorten med 279 KOL tilfælde. Den aldersstandardiserede prævalens af KOL var 5,0 % (95 % CI: 5,0;5,0) og signifikant lavere blandt kvinder 4,6 % (95 % CI: 4,6;4,6) sammenlignet med mænd 5,0 % (95 % CI: 5,0;5,0). Den justerede odds ratio (ORadj) fra den mixed model regressionsanalyse var for en medium (5-14 år) VGDF eksponering 1,61 (95 % CI: 1,03;2,51), og for høj (≥15 år) organisk støv eksponering ORadj 1,56 (95 % CI:

1,09;2,24). Eksponeringsniveauerne afspejlede yderligere signifikante tendenser i disse eksponeringer, henholdsvis p=0,031 og p=0,017.

Artikel II inkluderede kvinderne (N=1626) fra baseline kohorten. I alt havde 279 kvinder en relevant erhvervsmæssig eksponering og 76 kvinder havde KOL. Den erhvervsmæssige eksponering blev dikotomiseret til, om kvinderne havde haft en erhvervsmæssig eksponering eller ej. Den mixed model regressionsanalyse viste en øget association med KOL for VGDF og organisk støv eksponering med henholdsvis ORadj 1,98 (95 % CI: 1,06;3,69) og 2,05 (95 % CI: 1,04;4,08). Ved de to eksponeringer blev PAF henholdsvis estimeret til at være 14 % og 15 %.

Artikel III inkluderede ikkerygerne (N=1575) fra baseline kohorten. Blandt ikkerygerne havde 658 (42 %) en erhvervsmæssig eksponering og 26 havde KOL svarende til en prævalens på 1,7 %. Den erhvervsmæssige eksponering blev dikotomiseret til, om ikkerygerne havde haft en erhvervsmæssig eksponering eller ej. I den mixed model regressionsanalyse havde ikkerygerne eksponeret for VGDF og organisk støv en øget association med KOL med henholdsvis ORadj 3,69 (95 % CI: 1,36;10,04) og 2,94 (95 % CI: 1,05;8,22). PAF for KOL blandt ikkerygere forårsaget af en erhvervsmæssig eksponering var 48 % (95 % CI: 30;65) for VGDF og 41 % (95 % CI: 19;62) for organisk støv.

Artikel IV fokuserede på den fire-årige incidens af KOL, samt det årlige fald i lungefunktionen i det longitudinelle studie. De der havde KOL ved baseline blev ekskluderet (n=120) så 2624 blev inkluderet i studiet. Den årlige gennemsnitlige (± standardafvigelse (SD)) ændring i lungefunktionen blandt mænd var ΔFEV_1 -50 ml/år (±94) og ΔFVC -58 ml/år (±133), og for kvinderne var det henholdsvis -31 ml/år (±69) og -38 ml/år (±105). Analyserne af det årlige fald i lungefunktionen var ikke statistisk signifikante. Incident KOL blev identificeret hos 38 deltagere, og den aldersstandardiserede incidens var 0,9 % (95 % CI: 0,9;0,9) (mænd 1,0 % (95 % CI: 1,0;1,0), kvinder 0,7 % (95 % CI: 0,7;0,7)). Fra den mixed model regressionsanalyse var den justerede incidens rate ratio (IRR) for erhvervsmæssig eksponering associeret med KOL; lav (<5 år) VGDF eksponering 3,71 (95 % CI: 1,17;11,8), høj VGDF eksponering 2,62 (95 % CI: 1,06;6,48), lav organisk støv eksponering 3,24 (95 % CI: 1,07;9,83), dog uden klare eksponerings-respons sammenhænge.

Resultaterne fra artiklerne inkluderet i denne afhandling indikerer at en erhvervsmæssig eksponering er associeret med KOL. KOL var ligeledes associeret til den erhvervsmæssige eksponering blandt ikkerygere og kvinder. Vi fandt eksponerings-respons relationer i tværsnitsstudierne, der dog ikke blev understøttet i de longitudinelle analyser. VGDF eksponeringen bestod overvejende af organisk støv. Resultaterne er i overensstemmelse med andre internationale studier. Imidlertid var de estimerede PAF højere blandt ikkerygere sammenlignet med andre studier, hvorimod vi ikke har kendskab til andre sammenlignelige estimater af PAF blandt kvinder. På trods af den korte opfølgnings tid påviste de longitudinelle analyser en association imellem erhvervsmæssig eksponering og incident KOL.

Dette studie understreger den store indflydelse erhvervsmæssig eksponering for VGDF og organisk støv har på KOL, også blandt ikkerygere og kvinder. Disse fund fra det danske arbejdsmarked, kunne indikere at selv lave erhvervseksponeringer kan have betydning for udviklingen af KOL. Bevidstheden om disse resultater bør resultere i et forebyggende arbejde for at eliminere den erhvervsmæssige KOL og generelt forbedre folkesundheden.

ABBREVIATIONS

ATS	American Thoracic Society
CI	Confidence Interval
CNV	Copy Number Variation
COPD	Chronic Obstructive Pulmonary Disease
CPR	Danish Civil Registration
DALY	Disability-Adjusted Life Years
DISCO-88	Danish edition of the International Standard Classification of Occupations – edition 1988
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in the first second of expiration
FVC	Forced Vital Capacity
GBD	Global Burden of Diseases, Injuries, and Risk Factors Study
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner
GPP	General Practitioners Practice
GWAS	Genome-Wide Association Study
IRR	Incidence Rate Ratio
ISCO-88	International Standard Classification of Occupations – edition 1988
ISCO-88 (COM)	The European Union version of ISCO-88
LLN	Lower Limit of Normal
N	Number included
NCPS	The North Jutland COPD Prevention Study
OR	Odds Ratio
ORadj	Adjusted Odds Ratio
PAF	Population Attributable Fraction
qPCR	Quantitative Polymerase Chain Reaction
ROS	Reactive Oxygen Species
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
VGDF	Vapour, Gas, Dust and Fume

1. INTRODUCTION

1.1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines chronic obstructive pulmonary disease (COPD) in these phrases:

> ‘Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases’ (1).

This description emphasises the high prevalence of COPD. The latest Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) from 2010 globally rank COPD as 3rd in causes of age-standardised deaths only exceeded by ischemic heart disease and stroke, Figure 1.1 (2). Thus, passing the 2030 projected 4th mortality rank from 2006 (3). The burden of COPD is not restricted to mortality moreover disability is of major concern in COPD. Estimates from GBD rank Disability-Adjusted Life Years (DALY) quantifying the burden of disease from combined mortality and morbidity as well (4). In 2010 COPD by DALY was ranked as 11th in Western Europe and as 4th in Denmark (globally 7th). In Denmark DALY caused by COPD rank above e.g. lung cancer, stroke and road injury (5). Furthermore, COPD patients have a wide range of co-morbidities as e.g. cardiovascular diseases, osteoporosis, depression and lung cancer (1).

The economic costs caused by COPD have additional consequences for the society and the patients, as well as their spouses consisting of health-related contacts, medication use and higher socioeconomic related costs (6,7).

The most important tool to assess COPD is evaluating the lung function by spirometry. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) have collectively published an updated standardisation of spirometry (8). The individual airflow depends on sex, age, height and ethnicity and is compared to a normal reference population. During lifetime a normal lung function development is described by periods of growth (approx 18-20 yr), plateau (approx 20-35 yr) and decline as a trait of normal ageing (9). In theory, all three phases could be affected by exposures and implications for COPD development by decreased peak, shortened plateau or accelerated decline, respectively (10).

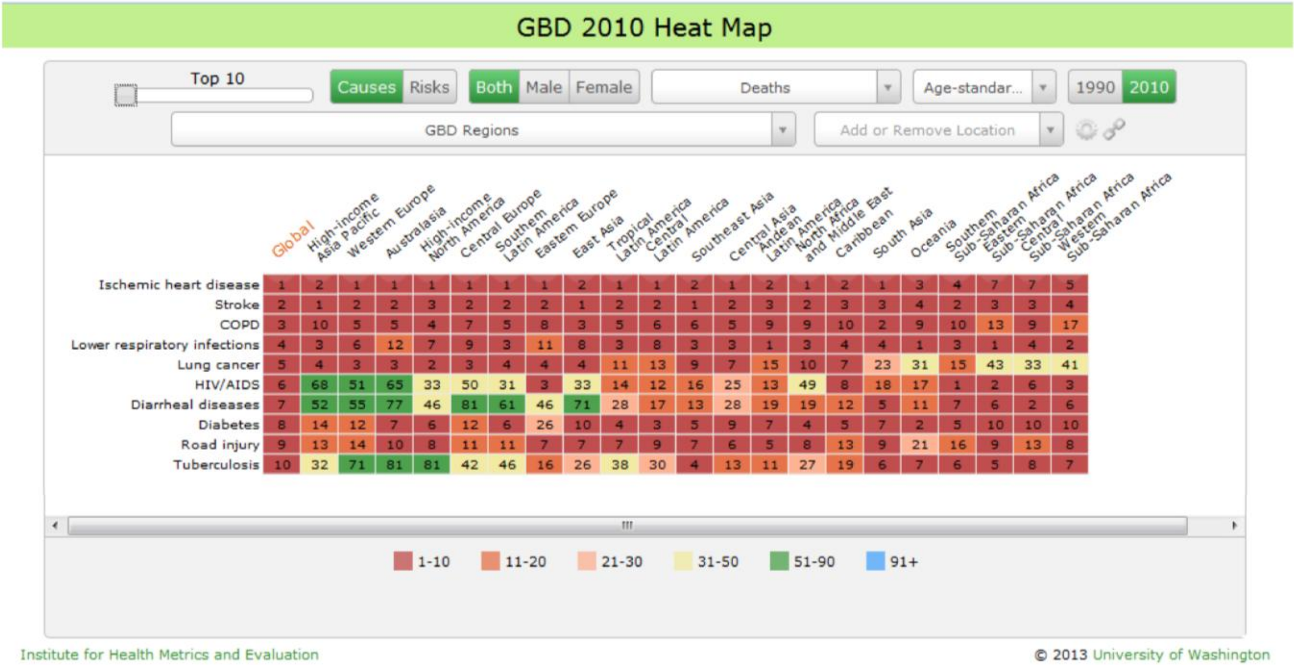

Figure 1.1: The Global Burden of Disease Heat Map (screenshot), The Institute for Health Metrics and Evaluation, University of Washington (5), presents the top 10 rank of age-standardised deaths in 2010 by regions.

COPD is characterised by heterogeneous phenotypes in respect of the clinical presentation, physiology, imaging, response to therapy, decline in lung function and survival with diverse degree of disease progression (11,12).

Although COPD is a global disease there are differences in prevalence among gender and countries. The BOLD study summarised the COPD variation from population based studies from 12 cities across the world among subjects aged ≥40 years. The overall moderate COPD prevalence was 10.1% and varied along with city and gender. Men had a higher prevalence 11.8% (range: 8.5-22.2) compared to women 8.5% (range: 5.1-16.7) (13). Moreover, currently available treatments have minimal impact on progression of the disease (10).

1.2. ETIOLOGY AND PATHOGENESIS FOR COPD

COPD is a common and complex disease. Exposure to particles is the major risk factor for COPD and mainly considered as smoking, which is the most important causal factor for COPD development (10,14). Up to 25% of continues smokers develop COPD (15) and smoking is estimated to account for ≤80% of COPD cases (16). Nevertheless, other estimates report that worldwide up to half of COPD cases are due to non-smoking causes e.g.: exposure to biomass smoke; occupational exposure to vapour, gases, dust and fumes (VGDF); history of pulmonary tuberculosis or chronic asthma; outdoor air pollution; diet; genes; age; gender; lung growth; passive smoking; poor socioeconomic status and early life events (1,10,14,17,18). Time periods of exposures presumed to affect the normal lung function throughout the whole life-span is for example with genetics, air pollution, and passive smoke potential impairments, whereas personal smoking and occupational exposures begin later in life, as described and illustrated by Eisner (10). Although COPD is a disease primarily diagnosed at older ages, its origin might be present before birth by prenatal effects and in early childhood (18).

COPD is characterised by airflow limitation due to chronic inflammation in the airways, composed in three major clinical phenotypes: emphysema, chronic bronchitis and small airways disease (18,19). Although an approach towards multi-dimensional phenotyping (information from different scales: e.g. organ-person, tissue-organ, cell-tissue, gene-cell) is forthcoming to improve COPD outcome and move towards personalised medicine (20). A phenotype could be described as any observable characteristics that results from gene-environment interactions (20). Despite the chronic inflammation recognised in COPD, there is sparse knowledge about a possibly normal lower respiratory tract microbiota, maybe dysbiosis is a triggering event for COPD or a biomarker of more severe disease (21). Nevertheless, the microbiome in different parts of the COPD affected lung and at different COPD stages seems to be heterogeneous (21).

The immune response in COPD is disturbed with excess accumulation of neutrophils and macrophages in the lungs, unleashing a cocktail of proteolytic enzymes leading to uncontrolled tissue destruction (19). The cellular responses to environmental stressors are controlled by reactive oxygen species (ROS), which include free radicals (superoxide radical anion, nitric oxide, radical hydroxyl, etc.) and non-free radical reactive species (H_2O_2, hypohalides, peroxynitrite, ozone, etc.) and produce oxidative modification of biomolecules (22). There is evidence for an increased generation of ROS expressed as oxidative stress in COPD patients (23).

The exact pathways leading to COPD are unknown and one pathway alone will apparently not fully explain the COPD pathophysiology. The four main hypotheses are the protease-antiprotease hypothesis, the British hypothesis, the autoimmunity hypothesis, and the Dutch hypothesis (19).

Briefly described the protease-antiprotease hypothesis is that proteases break down the connective tissue (elastin) in the lung to induce emphysema as a description of the lung changes e.g. induced by deficiency of α-antitrypsin inhibitors in the serine proteases. In normal lungs the proteolytic activities are counteracted by antiproteases in the lung (19) and the importance of protease-antiprotease balance in the pathogenesis of emphysema is strengthen in a candidate gene study among Finnish construction workers (24).

The British hypothesis for COPD is explained by recurrent bronchial infections, also often seen in exacerbation. The chronic and progressive path of COPD is often aggravated by exacerbations as additional acute inflammation defined by GOLD as:

> ‘An acute event characterised by a worsening of the patient’s respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication’ (1).

Exacerbations are expressed as short periods of increasing symptoms often caused by bacterial and/or viral respiratory infection or environmental pollutants (25,26). Furthermore, the exacerbations are an important cause of the health impairment, morbidity and mortality in COPD (26).

The autoimmunity hypothesis reflects the similarities of pathologic and clinical characteristics with other autoimmune diseases in some self-perpetuating process that fuels the inflammatory response (19). Animal studies present strong evidence that chronic cigarette smoke exposure is sufficient to initiate an autoimmune response (27).

The Dutch hypothesis is that asthma and COPD have some common genetic and environmental risk factors (28). This was described in network overlap in pathobiology by Kaneko in the search for common pathways underlying asthma and COPD (29). A recent large Genome Wide Association Studies (GWAS) concluded that:

> 'Our findings either suggest that there is no common genetic component in asthma and COPD or, alternatively, different environmental factors, like lifestyle and occupation in different countries and continents may have obscured the genetic common contribution' (30).

The normal lung function is highly heritable involving several genes (31). Genes play a role in the COPD development as well. Although the best known genetic variant alpha-1-antitrypsin deficiency only account for few percent of COPD cases (32,33). Several studies have been performed to identify additional genetic variants accounting for COPD and several genetic variants have an impact on the COPD development (34), but in summary these genetic variants only account for few percent of the variance according COPD development. Nevertheless the genetic studies in COPD are important to reveal causal genetic variants to discover new molecular targets for prevention, diagnosis, and treatment (34).

Identification and reduction of risk factor exposures are key elements in prevention and treatment of COPD (1,14). As the accelerated rate of decline in the lung function levels off in smokers with smoking cessation (14).

1.3. OCCUPATIONAL COPD

COPD develops slowly and as the airflow obstruction is chronic with no reversion when exposure is discontinued, the occupational COPD is based on elevated prevalence and risk observed among exposed workers compared to non-exposed workers (35). Several studies and reviews have addressed the issue of occupational exposure and COPD development despite variable terminology, case definitions, and exposure assessment. Recently, a meta-analysis provided a pooled estimate from 11 studies for the association between VGDF and COPD, odds ratio (OR) 1.43 (95% confidence intervals (CI): 1.19;1.73) regardless of some methodological differences (36). However, only few population-based studies have addressed the issue of occupational exposure solely among women.

Some reviews have focused on selected exposures (37,38) while most have addressed a large variety of exposures from different occupational settings (35,39-48). In the eighties Becklake concluded that occupational exposure to dust and/or dust and fumes may have a causal link to the pathogenesis of COPD, often relying on studies in which work-related factors were included as confounders to be adjusted for in analyses of smoking effects (39,40). Among coal miners Coggon and Newman Taylor concluded that there was a significant association between exposure to coal dust and the development of chronic airflow obstruction (38). The reviews highly emphasis occupational exposure as a causal factor for COPD (35,41-45,47).

The question of causality is often based on Sir Bradford Hill’s criteria from 1965 of strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy (49). When the issue of causality is established or accepted the extent of occupational exposure to COPD can be recognised as the population attributable fraction (PAF). In this context PAF is the fraction of COPD cases that are preventable if all occupational exposures were eliminated (50). A review from the ATS quantified the work-related risk to the general population and concluded that approximately 15% of COPD could be attributable to occupational exposure (35), and the evidence is growing (44,45).

As smoking is an essential risk factor for COPD, the association of occupational exposure to COPD is especially interesting among never smokers. An ATS official statement on COPD among non-smokers from 2010 concluded there was sufficient evidence to infer a causal relationship between occupational exposures and development of COPD (10).

Nevertheless, the PAF is pointless if the actual exposure not is amenable to intervention. In a public health perspective the occupational exposure is potential to intervene at different levels by e.g. invention, education and rationale of personal protection and reduced primary exposure in general regulation of work conditions and procedures in prevention and modifying disability risk.

2. AIMS

The thesis aim to address the association between occupational exposure and COPD in a population-based cohort of Danes aged 45-84-years.

The specific aims for the included original research articles or manuscripts in this thesis are specified for each included articles; Paper I-IV:

Paper I — The aim was to estimate the prevalence of COPD and analyse the association between COPD and prior occupational exposure to vapour, gases, dust and fumes (VGDF).

Paper II — The aim was to estimate the prevalence of COPD, and analyse the association and population attributable fraction of occupational COPD among women.

Paper III — The aim was to analyse for the association between occupational exposure and COPD among never smokers and estimate the corresponding population attributable fraction of the occupational exposure.

Paper IV — The aim was to analyse for changes in lung function over time and estimate the incidence of COPD and associations to VGDF in a longitudinal study.

3. MATERIAL AND METHODS

3.1. DESIGN AND SETTING

The study is based on data from the North Jutland COPD Prevention Study (NCPS) (51). NCPS is a population-based cohort with baseline data collected in the period October 2004 - September 2006. The geographical setting at baseline was outlined as two former counties in Denmark; North Jutland and Viborg. Aalborg is the largest city in the area with approximately 120,000 inhabitants in 2004 (Figure 3.1). In January 2005 these two counties together counted approximately 299,000 inhabitants in the study age band of 45-84 year old participants, representing 14% of Danes in this age group.

In Denmark all citizens have free access to medical care provided by a general practitioner (GP). All 480 GPs in the two counties were invited to contribute in the recruitment of participants to the NCPS. In the end 155 GPs (32%) were interested and willing to invest their time and involvement in the study. The 155 GPs were situated in 89 practices (GPP) with a mixed urban and rural distribution (Figure 3.1).

Figure 3.1: Geographical setting of the study. Left; Denmark with the two counties highlighted. At the top is North Jutland county and below Viborg county. Right; Each participating general practitioner practice (89) marked in an enlarged copy of the two counties (84 marks and 5 parallel addresses).

3.2. POPULATION

3.2.1. BASELINE

The Danish individual personal 10-digit Civil Registration System (CPR) was used to select a random sample of persons aged 45–84 from each GP. The sample was age and sex stratified with an overweight of elderly and men, based on the expected Danish prevalence of COPD in 10-year groups (52). From each GP 86 subjects were randomly selected in the Civil Registration System. Nevertheless, some GPs were unable to accomplish the amount of subjects in the selected age and sex distributions entailing missing invitations (n=243).

The 13087 selected subjects received an invitation by mail in which they were requested to contact their general practitioner in order to participate in the study. With a response rate at 36%, 4742 participants entered the study. Participants with a prior lung cancer were excluded (n=25), leaving 4717 participants for analyses at baseline. The flow chart illustrates the entire enrolment of the baseline study population and throughout the follow-up study (Figure 3.2).

3.2.2. FOLLOW-UP

Follow-up data were collected between October 2008 and August 2010 in the same way as baseline data. Four GPP were not motivated to participate in the follow-up study, which excluded their 206 eligible baseline participants. These participants were assigned as non-responders, although they didn’t receive an invitation at follow-up. Additionally 207 baseline participants passed away before the time of follow-up. The remaining participants included at baseline were sent a mail invitation and requested to contact their general practitioner again to participate in the follow-up study. The response rate at follow-up was 58%. The follow-up data consisted finally of 2624 participants, including 33% females. In the final follow-up population seven were excluded due to missing lung function test at baseline and 120 excluded due to COPD at baseline. COPD at baseline was defined by spirometry according to the method of Lower Limit of Normal (LLN), further described in paragraph 3.5, page 31.

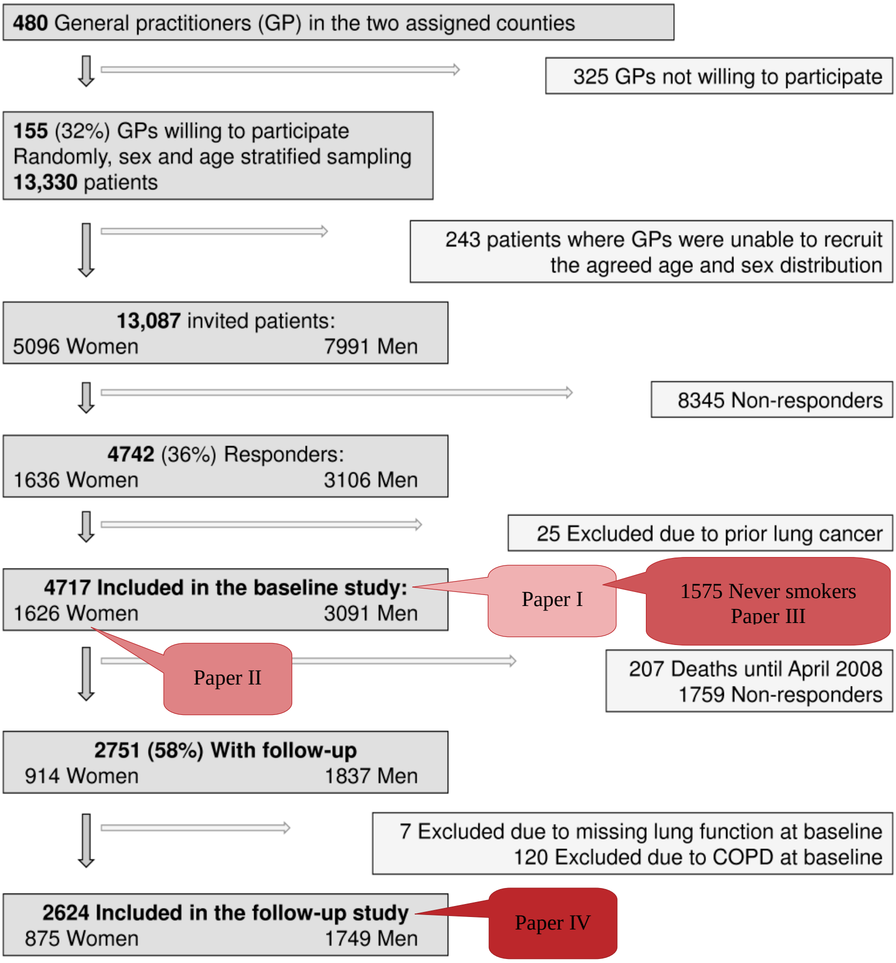

Figure 3.2: Flow chart of the study population throughout follow-up, 2004-2010, and indication of the populations included in each of the Papers in the thesis.

3.3. DATA

Baseline data consisted of a self-administered questionnaire, medical examination and a blood sample. The questionnaire included items of education, work, family history of lung disease, medical information, smoking and alcohol habits, asthma and allergy. The medical examination included blood pressure, height, weight, waist and hip measurements, and spirometry tests to assess the lung function by forced expiratory volume per second (FEV_1) and forced vital capacity (FVC). Asthma was assessed by the question: “Have you ever had asthma?” The form for medical examination and the questionnaire are included as Appendix A, page 65 (in Danish). The established biobank were collected for later analysis. Thus venous blood samples were collected in EDTA glasses (anticoagulant) and stored as whole blood at -20°C and stored at the Laboratory of Stem Cell Research, Aalborg University, Denmark.

Longitudinal data was collected approximately four years after the baseline data and consisted of a less comprehensive questionnaire and a similar medical examination without a new blood sample. The form for medical examination and the questionnaire are included as Appendix B, page 71 (in Danish).

3.4. SPIROMETRY AND REFERENCE VALUES

Pulmonary function tests were accomplished at the GP visits at baseline and follow-up by spirometry. The spirometry was performed by the GP or a trained member of the practice staff with the general practitioners own spirometer. Volume and time calibration of the spirometers was performed before study start and every six months by trained staff using a one litre syringe. Adequate spirometry test instructions followed the statement from the ERS (53) and the standard from ATS (54). For participants with a FEV_1/FVC ratio below 0.70 a reversibility test was performed with eight inhalations of Combivent (1 dose=100 μg salbutamol and 20 μg ipratropium) and assessed after 30 minutes.

The Global Lung Function 2012 Equations (55) in the “GLI-2012 Desktop Software for Large Data Sets version 1.3.4 build 3” (56) was used as reference population. This equation takes age, sex and ethnicity into account to estimate the subsequent applied z-scores.

Based on the longitudinal data we assessed the annual decline in lung function and incident cases of COPD. In that cohort we excluded baseline COPD cases. The individual annual change in lung function was expressed by FEV_1 and FVC and calculated as follow-up data minus baseline data divided by the individual follow-up time.

3.5. COPD DEFINITION

We defined COPD by lung function measurements; FEV_1 and FVC. To assess the COPD diagnose the method of LLN was used. This approach for the FEV_1/FVC ratio is recommended concurrently by the ERS and ATS (57). In a screening setting of normal subjects the LLN is the 2.5^{th} centile (z-score = -1.96) (55). To distinguish subjects with at least moderate airway obstruction we added the screening criterion of the LLN for FEV_1 of a z-score = -2.0 (rounded 2.5^{th} centile) as recommended by Quanjer et al. (58). COPD defined by LLN was estimated using the pre-bronchodilator values.

Data was additionally presented based on the GOLD criteria with a fixed FEV_1/FVC ratio<0.70 and FEV_1< 80% of the predicted value (moderate airways obstruction; GOLD 2+) (3). This additional definition was included for possible comparison with prior studies and for discussion of methods. COPD defined by GOLD was estimated using the post-bronchodilator values if the pre-bronchodilator FEV_1/FVC ratio was <0.70 otherwise pre-bronchodilator values were used.

3.6. SMOKING

Smoking habits were assessed from the baseline and follow-up questionnaires. Different smoking variables were estimated; smoking status, duration of smoking and a cumulated smoking exposure. Smoking status was reported in a dichotomous variable as never-ever smoking or at three levels never-ever-current smoking. The smoking duration was assessed as years of smoking, and the cumulated smoking exposure as smoked pack-years. Pack-years were defined as the number of cigarettes smoked per day multiplied by the number of years smoked divided by 20. Pack-years were reduced to three levels of smoked pack-years: below 10, 10-20, and above 20 pack-years, respectively. In conversion of different types of smoking to the equivalent amount of cigarettes the clinical used equation from Aalborg University Hospital was used, as stated by the following equations: one cheroot=three cigarettes; one cigar=four cigarettes, one pipe bowl=three cigarettes, and a package of pipe tobacco (50 gram)=17 pipe bowls.

3.7. OCCUPATIONAL EXPOSURE ASSESSMENT

The occupational exposure assessment was based on a self-administered questionnaire validated by additionally restriction to a priori specialist identified jobs with an occupational exposure.

3.7.1. SPECIALIST

Two specialists in occupational medicine addressed an occupational exposure to the Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) (59). A priori all 372 DISCO-88 codes were evaluated and codes with known presence of occupational exposure to dust, gas, vapours and or fumes were identified. Final decision of identified codes was agreed upon by the two specialists. The final list of the 72 identified DISCO-88 codes is included as Appendix C, page 75 (in Danish). The self-reported jobs with an occupational exposure were then restricted to the selected DISCO-88 codes. The 72 DISCO-88 codes were distributed as 34 within organic dust, 20 within inorganic dust, 3 within fume/gas, 5 within vapour, and additional combination of exposures; 2 within organic and inorganic dust, 7 within inorganic dust and fume/gas, and 1 within inorganic dust, fume/gas and vapour. The complete list with English job descriptions is included in Paper I, Supplementary Table S.

3.7.2. QUESTIONNAIRE

The participants were asked for job titles and duration of their longest held jobs with an exposure to organic dust, inorganic dust, fume/gas, and or vapour, respectively. Furthermore, for each exposure category the participants could state up to three longest held job titles and appertaining durations. Thus, each participant could in theory state three jobs in each of the four exposure categories equal to 12 held jobs with an occupational exposure. Each job was reported with duration in five-year spans: ≤5 years, 5-9 years, 10-14 years, 15-19 years, and ≥20 years. The total duration of employment per exposure category was then calculated to define four levels of cumulated duration of exposure: no exposure (0 years), low exposure (<5 years), medium exposure (5-14 years), and high exposure (≥15 years). For each of the exposure categories, the total period of employment was calculated by adding the mean years of each stated employment as illustrated with different job combinations in each row in Figure 3.3.

Exposure	1	2	3	Time	Mean
NO	O	O	O	0	0
LOW	L	O	O	>0-<5	<2.5
	L	L	O	>0-<10	<5
MEDIUM	L	L	L	>0-<15	<7.5
	M	O	O	5-14	9.5
	M	L	O	>5-18	<12
	M	L	L	>5-22	<14.5
HIGH	M	M	O	10-28	19
	M	M	L	>10-32	<21.5
	M	M	M	15-42	28.5
	Any high combination			min. 15	min. 15

Figure 3.3: Achievable job combinations within each exposure category. NO/O: no occupational exposure; LOW/L: low occupational exposure; MEDIUM/M: medium occupational exposure; HIGH: high occupational exposure. Time: years. Mean: mean years worked with a particular occupational exposure, marked means indicate the defined exposure levels.

In the combined VGDF exposure the level of occupational exposure was estimated in a slightly different way. When summarising the four exposure categories in one overall combined VGDF occupational exposure according to the possible exposure from each specific exposure category, the "low exposure" was defined to have specific low exposures only, "medium exposure" to have specific medium exposure, but no high exposures, and finally "high exposure" to have any specific high exposure. This is illustrated in Figure 3.4.

	1	2	3	4
No	0	0	0	0
Low	Any low combination without medium or high exposure			
Medium	Any medium combination without high exposure			
High	Any high combination			

Figure 3.4: Structure of the combined vapour, gas, dust and fume (VGDF) exposure. 1-4 reflect the four exposure categories of organic dust, inorganic dust, fume/gas, and vapour, respectively. No/0 illustrates no occupational exposure. Small letters low, medium, and high express the level of occupational exposure in each exposure category. Capital letters Low, Medium and High express the level of the combined VGDF occupational exposure.

3.8. DATA MANAGEMENT

In data management the a priori identified DISCO-88 codes were assigned to jobs included in the DISCO-88 description from Statistics Denmark (59). For each participant all applicable DISCO-88 codes within the four exposure categories were assessed at the same time to provide the best job indication. We experienced several participants who assigned jobs in mistaken exposure categories e.g. all exposed jobs reported at the first occasion in the questionnaire (e.g. welders exposed to organic dust). Additionally, in no accordance with the specialist identified DISCO-88 codes many more jobs were assigned as occupational exposed. Thus the specialist identified DISCO-88 codes persistently exceeded the self-reported occupational exposure in the exposure assessment. The final list of included job titles within each DISCO-88 code is included as Appendix D (in Danish); D.1: Organic dust, page 79, D.2: Inorganic dust, page 84, D.3: Fume/gas, page 88, and D.4: Vapour, page 91.

No general imputation of missing data was conducted, but few essential missing data were imputed in the data set. Height was missing or evidently wrong in four participants, one was imputed from follow-up data and the others estimated as a mean height of similar participants according to sex, age and weight. In some questionnaires there was discordance between the stated smoking status and the present number of smoked cigarettes; in these cases the number of smoked cigarettes exceeded the stated smoking status.

3.9. STATISTICS

Statistical analyses were conducted in Stata 12.1 (StataCorp LP, 2011). The significance level was set at 5%. The 95% CI was calculated using a normal approximation. The chi-square test and Fishers exact test for categorical variables was used to assess differences between sub-groups of the study population. While non-parametric analysis of Kruskal-Wallis was used for non-normally distributed data. The McNemar test was used for matched data to compare the two methods of assessing COPD; the LLN and GOLD methods as defined earlier. Baseline COPD prevalence was age-standardised to the Danish population, January 2006. At baseline (Paper I-III) associations of occupational exposure to COPD were analysed univariate and in mixed random effect logistic regression models (60) with GPP as random variable. Likelihood ratio tests were performed for possible interaction of variables in the models. The PAF was estimated on the basis of the adjusted OR by the following equation; proportion of cases exposed*(OR-1)/OR (50). In the equation OR was used as a proxy for the relative risk.

3.9.1. PAPER I

The mixed regression model was adjusted for pack-year, sex and age as fixed effects. Sensitivity analyses were performed by recoding all the missing occupational exposures (i) into no exposure and (ii) into high exposure, or by (iii) excluding all participants with prior self-reported asthma.

3.9.2. PAPER II

The mixed regression model was adjusted for pack-year and age as fixed effects. Sensitivity analyses were performed by (i) excluding all participants with self-reported asthma and (ii) include mild COPD in the LLN COPD definition (FEV_1/FVC 2.5th centile, but lacking the FEV_1 LLN criteria) and (iii) exclude women with a tentative occupational exposure.

3.9.3. PAPER III

Among the never smokers in Paper III the mixed regression model was adjusted for sex and age as fixed effects. Sensitivity analyses were performed by excluding all participants with self-reported asthma, and additional adjustment for passive smoking.

3.9.4. PAPER IV

The annual change (Δ) in FEV_1 and FVC was reported as mean and standard deviations (SD), and analyses of variance were used to compare groups of normally distributed means. The annual change in FEV_1 and FVC were stratified by age ($<$ and $\geq$ 60 year at follow-up). The choice of 60 years was applied to take the possibility of voluntary early retirement pension in these birth cohorts into consideration. Thus the youngest group was considered as a proxy for an ongoing working population throughout the follow-up period if they reported no occupational change in-between baseline and follow-up. The COPD incidence was age-standardised to the Danish population, January 2010. When estimates were based on the GOLD defined COPD, additional 120 participants with baseline GOLD defined COPD were excluded. Mixed Poisson regression model with GPP as random variable was used to estimate the association between incident COPD and occupational exposures with adjustment for pack-years, sex and age, reported as incidence rate ratio (IRR). Due to few COPD cases in the youngest age groups, age was included as a continuous variable. Additionally, the IRR was adjusted for asthma status in-between baseline and follow-up. Analyses of the combined VGDF occupational exposures were additionally restricted to organic dust, as organic dust was the main single occupational exposure group. Data didn’t reveal the power to analyse the other sub-groups of occupational exposure.

3.10. ETHICS

The NCPS-study has been performed in accordance to the Helsinki Declaration and approved by the Danish Scientific Ethics Committee (VN2003/62) and the Danish Data Protection Agency (updated in 2007 before follow-up: 2007-41-1576). Written informed consent was obtained from all participants.

4. SUMMARY OF RESULTS

The main results from each Paper are summarised below while more detailed results are available in the appended Papers (Appendices E-H), nevertheless the occupational exposure is described more detailed than in the Papers. This section will focus on COPD defined by LLN, while association to the GOLD defined COPD, additionally, is described in the appended Papers. We observed no statistical significant interaction terms among the used variables in the different models. Furthermore, few additional PAF results are presented at this point, as these were not included in Paper I; although they are important for the external validity and evaluation of the study.

The PAF caused by occupational exposure in COPD was initially addressed among women and never smokers (Paper II and III), but not in the whole study population (Paper I). The PAF of an occupational exposure to VGDF calculated among the whole study population in contribution to COPD was estimated to 15% (95% CI: 3;28) and similar when limiting the exposure to the main single exposure of organic dust, 15% (95% CI: 3;27).

4.1. OCCUPATIONAL EXPOSURE

The occupational exposure assessment was equal in all four papers. As described in Paper I 372 DISCO-88 codes excist and 72 of them were a priori selected as exposed to any VGDF. In this study population only 54 (75%) DISCO-88 codes were identified. The included codes were distributed as 27 of the 34 identified DISCO-88 codes with relevant exposure to organic dust, likewise 12 of 20 to inorganic dust, 2 of 3 to fume/gas, 5 of 5 to vapour, 0 of 2 to combined organic and inorganic dust, 7 of 7 to combined inorganic dust and fume/gas, and 1 of 1 to combined inorganic dust, fume/gas and vapour (Appendix E: Supplementary Table S1).

About half of the population, 49%, reported no DISCO-88 code with relevant exposure, 31% reported one DISCO-88 code with relevant exposure, and 15% (n=693) reported between two and six DISCO-88 codes with relevant exposures, while 5% did not answer the occupational question. However, there were significant gender differences in the assessed occupational exposure, $p<0.001$ (Table 4.1). The majority of women (75%) had no relevant occupational exposure to VGDF, while men more often experienced exposures from more than one exposure category (Table 4.2) and 39% had a relevant high exposure to VGDF (Table 4.3). Organic dust was the most frequent occupational exposure in both men (56%) and women (19%), and out of all participants with a combined VGDF exposure, 80% had an organic dust exposure among the men and 90% among the women. The distribution of the occupational exposures is separately illustrated by sex and level in Paper I (Appendix E: Figure 2). As addressed in Table 4.2 the figure underlines the fact that many participants (15%), especially men, have several exposures since the exposure pillars in the figure section with VGDF are less than the sum of the specific exposure pillars within each category.

Table 4.1: Number of assigned DISCO-88 codes by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Number of assigned DISCO-88 codes				
0	1226	(75)	1104	(36)
1	248	(15)	1203	(39)
2	29	(2)	445	(14)
3	2	(0.1)	150	(5)
4	0	-	52	(2)
5	0	-	13	(0.4)
6	0	-	2	(0.1)
No answer	121	(7)	122	(4)
Total	1626		3091	

DISCO-88: The Danish adaptation of The International Standard Classification of Occupations, revision 1988 (DISCO-88) (59).

Table 4.2: Number of assigned VGDF categories by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Number of assigned VGDF categories				
0	1226	(75)	1104	(36)
1	265	(16)	1338	(43)
2	14	(1)	373	(12)
3	0	-	132	(4)
4	0	-	22	(1)
No answer	121	(7)	122	(4)
Total	1626	(100)	3091	(100)

VGDF: Vapour, gas, dust and or fume.

Table 4.3: Distribution of the combined VGDF assessed exposure by gender in the study population, N=4717.

	Women		Men	
	n	(%)	n	(%)
Dose of VGDF defined by time				
No exposure	1226	(75)	1104	(36)
Only low exposure	61	(4)	309	(10)
Medium, exposure (and no high)	63	(4)	360	(12)
Any high exposure	155	(10)	1196	(39)
No answer	121	(7)	122	(4)
Total	1626	(100)	3091	(100)

VGDF: Vapour, gas, dust and or fume. Low: Exposure, but <5 years. Medium: 5-14 years of exposure. High: ≥15 years of exposure.

4.2. PAPER I

Paper I included the whole baseline study population (N=4717). The lung function test was missing in 20 participants leaving 4697 with a pre-bronchodilator spirometry. The age-standardised LLN defined prevalence of COPD was 5.0% (95% CI: 5.0;5.0) and significant lower among women compared to men, 4.6% (95% CI: 4.6;4.6) and 5.0% (95% CI: 5.0;5.0), respectively (Appendix E: Table 2), equal to 279 participants with COPD.

In a matched comparison of the two methods for defining COPD (LLN and GOLD) there was a significant difference with 173 discordant diagnoses between the LLN (17 only COPD by LLN) and GOLD (156 only COPD by GOLD) definitions (Appendix E: Table 3).

The associations between occupational exposure to VGDF or the organic dust variable and COPD, revealed from the mixed regression model, were increased for the occupational exposures. As well as for the additional known risk factors for COPD as smoking, age and gender (Appendix E: Table 4). The adjusted odds ratio (ORadj) for medium VGDF exposure was 1.61 (95% CI: 1.03;2.51), while the ORajd for high organic dust exposure was 1.56 (95% CI: 1.09;2.24). Significant trends in exposure level were also present in these associations, p=0.031 and p=0.017, respectively. As agriculture was the main exposure in the organic dust category with 1495 out of 1926 occupational reports (78%) the analyses were restricted to this exposure as well, and ORadj and trend remained significant; 1.59 (95% CI: 1.08;2.33), p<0.02, respectively. No associations to COPD were seen in the other occupational exposures of inorganic dust, fume/gas and vapour in the study

4.3. PAPER II

Paper II included the women (N=1626) from the baseline study population. Among the women 35% of the identified 72 DISCO-88 codes were applied (25 DISCO-88 codes) and the distribution is described in Table 4.4 with the majority of codes and participants in agriculture. In all, 279 women were assigned with a relevant occupational exposure by the specialist assessed exposure. Lung function measurements were present in 1617 with a pre-bronchodilator spirometry and 76 had COPD defined by LLN.

In the paired comparison between the two criteria for defining COPD there was a significant difference in the oldest age group (75-84 years) where more subjects had COPD using the GOLD definition (15.3%) compared to the LLN definition (7.5%), $p<0.001$.

Table 4.4: Distribution of the a priori selected DISCO-88 codes with known relevant occupational exposure to organic dust, inorganic dust, fume/gas, and vapour, among the 1626 participating women*, and job descriptions of the most frequently applied codes (≥ 10 participants).

Job description†	DISCO-88	Assigned exposure				
		Organic dust	Inorganic dust	Inorganic dust and Fume/gas	Fume/gas	Vapour
Field crop and vegetable growers	6111	*12*				
Dairy and livestock producers	6121	*17*				
Market-oriented crop and animal producers	6130	*138*				
Welders and flamecutters	7212				*20*	
Wood-products machine operators	8240	*10*				
Fibre-preparing-, spinning- and winding-machine operators	8261	*17*				
Farm-hands and labourers	9211	*53*				
Number of applied DISCO-88 codes among the women (sum 25)	25	14	4	3	1	3
Number of applied DISCO-88 codes among the women with ≥ 10 participants	7	6			1	

DISCO-88: Danish adaptation of The International Standard Classification of Occupations, revision 1988 (59).
*Missing occupational information, n=*121*. †Statistics Denmark (3 April, 2014): http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88/Sammenlignende.aspx. *Italic; Number of participants.*

The occupational exposures were dichotomised as never or ever occupational exposed women to achieve a better power in the study, due to few exposed women. The results from the mixed model regression analyses on the association between occupational VGDF, organic dust exposure, and COPD are presented in Paper II (Appendix F: Table 2). The ORadj in VGDF and organic dust exposure revealed a significant increased association to COPD, 1.98 (95% CI: 1.06;3.69) and 2.05 (95% CI: 1.04;4.08), respectively. The study PAF for COPD was estimated to be 14% in the VGDF exposure and 15% when restricted to the organic dust exposure. Whereas too few women had an occupational exposure to inorganic dust (n=9), fume/gas (n=23), and vapour (n=17) for analyses as illustrated in Paper II (Appendix F: Figure 2).

In sensitivity analyses the occupational specialists identified 24 women with a tentative farming exposure as ‘assisting wife’, when excluding this group in the analyses of organic dust the association was maintained; ORadj 2.15 (95% CI: 1.06;4.37). Excluding women with prior asthma (n=174) increased both associations to occupational VGDF and organic dust exposure to COPD, ORadj 2.81 (95% CI: 1.36;5.79) and 2.99 (95% CI: 1.37;6.55), respectively.

4.4. PAPER III

Paper III included the never smokers from the baseline study population (N=1575). Occupational exposure were present in 658 (42%) of the never smokers in between 1 (72%) and 5 jobs. COPD defined by LLN was present in 26 participants equal to a prevalence of 1.7%.

Table 2 in Paper III (Appendix G) show the adjusted associations between the occupational exposures and COPD. Participants exposed to VGDF and organic dust had an increased risk of COPD, ORadj 3.69 (95% CI: 1.36;10.04) and 2.94 (95% CI: 1.05;8.22), respectively. An important confounder among never smokers is passive smoking, but only few (n=45) had never experienced this. Passive smoking was not associated to COPD and only to a minor extent additional adjustment changed the estimates. Excluding 145 never smokers with prior self-reported asthma (reported as never or ever) in the analyses provided similar associations; VGDF: ORadj 2.64 (95% CI: 0.70;9.92), organic dust: ORadj 3.43 (95% CI: 0.86;13.70).

The study PAF for COPD among never smokers caused by occupational exposure was 48% (95% CI: 30;65) for VGDF exposure and 41% (95% CI: 19;62) for organic dust exposure.

4.5. PAPER IV

Paper IV was the four-year longitudinal study with follow-up data from 2008/2010 focusing on COPD incidence and annual decline in lung function. The mean period of follow-up time was 3.7 years (SD 0.35; range 2.4-5.0 years) and equal across genders. Follow-up participants and non-participants were compared in the Paper (Appendix H: Table 1) and equal according occupational exposure, although participants were younger, had better lung function and smoked less. COPD cases at baseline were excluded (n=120) thus 2624 were eligible, but additional 28 lacked spirometry at follow-up and finally 2596 participants with spirometry were included.

Decline in lung function was addressed in the Paper (Appendix H: Online Supplementary Table S1). Briefly the overall annual mean (±SD) change in lung function in men was ΔFEV_1 -50 mL/yr (±94) and ΔFVC -58 mL/yr (±133) and in women -31 mL/yr (±69) and -38 mL/yr (±105). No analyses reached statistical significance. In men (<60 years) with combined exposure from occupation and smoking there was a borderline trend in association in FVC (VGDF; p=0.11, organic dust; p=0.06) and a 2-fold decrease in FVC, and partly in FEV_1 when comparing non-smokers having no occupational exposure with smokers having an occupational exposure.

New-onset COPD was identified by spirometry in 1.5% (95% CI: 1.0;1.9) of subjects (n=38) (men 1.7% (95% CI: 1.1;2.4), women 0.9% (95% CI: 0.3;1.6)). The age-standardised estimates were 0.9% (95% CI: 0.9;0.9) (men 1.0% (95% CI: 1.0;1.0), women 0.7% (95% CI: 0.7;0.7)). In comparison of the two definitions of COPD there was a significant difference, p<0.01.

The IRRs from the regression analyses are summarised in the Paper (Appendix H: Table 3). In the adjusted IRR occupational exposures were associated with COPD; low VGDF exposure 3.71 (95% CI: 1.17;11.8), high VGDF exposure 2.62 (95% CI: 1.06;6.48), low organic dust exposure 3.24 (95% CI: 1.07;9.83), but with no clear exposure-response relation. As expected other known risk factors of COPD as smoking and age were associated to COPD as well. Sub-analyses were performed with adjustment for asthma status between baseline and follow-up. This increased the low VGDF association to IRR 4.57 (95% CI: 1.38;15.15) while the high exposure slightly decreased to IRR 2.43 (95% CI: 0.92;6.38), p= 0.07. A similar pattern was revealed for organic dust (low exposure IRR 3.77 (95% CI: 1.21;11.79).

5. DISCUSSION

In this population based study including both cross-sectional and longitudinal analyses the VGDF exposure consisted predominantly of organic dust. COPD was associated to occupational exposure also in subsets of never smokers and women, but without a clear exposure-response relation in the longitudinal analysis.

5.1. PAPER I

We found an age-standardised prevalence of COPD of 5.0%. This is in accordance to other studies from Europe and US where the prevalence is reported to be between 4.5 and 10% using different diagnostic criteria (61-65).

In the present study occupational VGDF and organic dust exposures were in a dose dependent manner associated to the prevalence of COPD. The associations were similar when restricting the analysis from organic dust exposure to agriculture exposure alone. The positive associations within the organic occupational exposure may reflect the dominating position of agriculture in Northern Denmark as the major occupation for exposure to VGDF in the study. Several cross-sectional studies have found an association between occupational organic dust exposure in agriculture and COPD (66-68). We found a weaker association between high organic dust exposure and COPD when excluding subjects with prior self-reported history of asthma ORadj 1.47 (95% CI: 0.92;2.34), trend p=0.15. In the SAPALDIA study, including only non-asthmatics, the incidence rate ratio was 2.76 (95% CI: 1.32;5.75) for COPD with any organic dust exposure in ever smokers (69). The differences in observation might be due to difference in the concentration of the exposure, low statistical power in our study or may reflect healthy-worker selection where subjects with possible prior asthma leave farming to more manageable jobs with lower occupational exposures.

The calculated PAFs of 15% in subjects exposed to both VGDF and organic dust were in accordance with prior estimates of the burden of occupational exposure (PAF not included in Paper I) (35,44,45).

5.2. PAPER II

The age-standardised prevalence of COPD among women was 4.6%, and in accordance with other studies from Europe and US where the prevalence in women is reported to be between 4 and 7% using different diagnostic criteria (62,64,65). Our findings is also in accordance with the data from the review by Halbert et al. that estimated a pooled female prevalence from 27 studies to be 5.6% (95% CI: 4.4;7.0) (70) and even more so when defining COPD as the clinical used $FEV_1/FVC<LLN$ 5^{th} centile (z-score < -1.64) and $FEV_1<LLN$ -2. Then the age-standardised prevalence was 6% (n=93).

The association between occupational exposure and COPD solely in women is studied by few when defining COPD on lung function measurements. Matheson et al. estimated a strong association between COPD and organic dust exposure among women, OR 7.43 (95% CI: 2.07;26.7), but this estimate was based on a broader definition of COPD (71). Studies by Beck et al. and Elwood et al. estimated a significant decline or lower FEV_1 among female cotton textile workers (72,73). We found stronger associations to COPD when excluding subjects with prior self-reported history of asthma. Our estimates are in accordance with the SAPALDIA study where only non-asthmatics of both genders were included. They found an incidence rate ratio of 2.76 (95% CI: 1.32;5.75) for any organic dust exposure in ever smokers and COPD (69). Although females have been shown to perform work with less respiratory hazards compared to males within the same occupation and industry (74) few studies have analysed for PAF for COPD associated to occupational exposure in females, and none in the same age group as in the present study. Blanc and Torén estimated in their review from 2007 PAF for COPD to be 0 and 1% (44), but these were based on a younger population exposed to dust, and gases and fumes (75). Our estimates (14% for COPD in exposed to VGDF and 15% in exposed to organic dust) are in correspondence with the 15% PAF for COPD calculated in former studies (76), but predominately based on men.

5.3. PAPER III

COPD was increased more than three times in never smokers when occupationally exposed to VGDF and three fold for organic dust despite the low prevalence of COPD (1.7%). However, the calculated associations between occupational exposure and COPD have wide CI due to few cases in each stratum. Our prevalence estimate was low compared with the prevalence in never smokers from the BOLD study (0-11%) (13). Here COPD was defined by GOLD criteria stage II or higher in a slightly younger population. When converting our prevalence estimate based on LLN criteria to GOLD criteria the prevalence of COPD increased to 3.4% reducing the difference in the prevalence between the studies. We have found the highest PAF among studies published in never smokers 48% (95% CI: 30;65) (63,76) and higher than the PAF 43% (95% CI: 0;68) from the study by Weinmann (77) a smaller case-control study with similar definitions of COPD by LLN and an expert assessed occupational exposure as in the present study.

However, a big Chinese population-based study including 6648 never smokers found no significant association between self-reported occupational exposure and COPD defined by LLN, OR 1.29 (95% CI: 0.92;1.81) (78). This might be a result of non-differential misclassification moving the risk estimate towards null by incorrectly label low or no exposure jobs in the high exposure group and vice a versa.

5.4. PAPER IV

The age-standardised four-year incidence of COPD was 0.9%. This is in accordance with results from the US ARIC study where the three-year incidence was 2%, though obstruction was defined by LLN 5th centile (79). We have applied the FEV_1/FVC LLN of 2.5th centile instead of the clinical used 5th centile to reflect a screening setting in our population-based study having no a priori indication of COPD.

The annual decline in FEV_1 and FVC revealed no statistical significance in any of the analysis. The short follow-up time and the observed wide range in variation might partly explain our findings. However, in men below 60 years of age the combination of occupational exposure and smoking caused a decline in FVC, with borderline statistical significant trends; VGDF p=0.11 and organic dust p=0.06. The study annual decline in lung function was lower, but with wider variation as compared with the ARIC study although our population was older (79). This might reflect differences in spirometry testing and equipment. However, ethnicity could also play a role. In the ARIC study 23% of the participants were black (79), compared to only Caucasians in our study.

Despite the short follow-up time prior occupational exposures were associated to incident COPD by 2-3 folds, but with no clear exposure-response relation. The ARIC study found no association with current or most recent occupation at baseline (79). In contrast, the SAPALDIA study found dose-dependent associations between VGDF in both LLN and GOLD defined COPD, and only highly exposed LLN were non-significant. The associations ranged from 1.1 to 4.0 (69) similar to the LNN association in the current study. Their occupational exposures were based on current job, duration of current job and a job exposure matrix. We used a cumulative job exposure from all held jobs and extracted the level of exposure based on mean total exposed years in the different jobs. These different approaches might explain the differences in associations. Furthermore, the differences could reflect national variation in the welfare system. In Denmark it might be easier to be retrained, change job conditions or job compared with Switzerland, thus the reason why we find the association more pronounced in the low occupational exposure group might be due to a healthy worker effect. The high effect in the low exposed group could also be a consequence of age differential work procedures. As for instance in farming the younger workers perform the most hard, dirty and dusty tasks, while the elderly will concentrate on less strenuous and cleaner job tasks.

The differences between LLN and GOLD might reflect that GOLD defines too many COPD cases alone according to their age, which might dilute the association to the working exposure. Additional adjustment for asthma status between baseline and follow-up increased the IRR among the low occupational exposures using the LLN approach. Thus the results after excluding asthmatics emphasise the assumed healthy worker effect as they have known symptoms and might have changed their work tasks or jobs to more manageable tasks or jobs with lower occupational exposures because of these symptoms.

5.5. METHODOLOGICAL ISSUES

5.5.1. COPD

In epidemiologic studies the definition of disease is often simplified and not identical to the corresponding clinical diagnose. We defined COPD by lung function measurements. There is no 'gold standard test' to assess COPD by spirometry. Nevertheless, the LLN approach is recommended concurrently by the ERS and ATS (57). As opposed to the GOLD fixed method which is somewhat biased by participants age, sex and height (80). This difference was also revealed in the present study with increased prevalence of COPD among the women in the oldest age group calculated by the GOLD method compared to the LLN method. The LLN definition ensures that the participants do have a degree of airflow obstruction outside accepted population norms. However, the 2.5^{th} centile as a diagnostic criterion is a conservative approach aiming to minimize the percentage of false positives at the expense of an increased number of false negatives, as the population-based study is comparable with a screening situation and not related to symptoms and diagnosing.

To assess the COPD severity the ATS/ERS recommendation utilise the fixed FEV_1 percent predicted (57). In the present study we have analysed the data based on the recommendation by Quanjer et al. They recently published a new grading of the obstructive lung disease that is clinically relevant and free of biases related to age, height, sex and ethnic group (58). Adding the restriction of FEV_1 z-score <-2 we obtain a group of subjects having moderate airways obstruction, corresponding to the ATS/ERS moderate airways obstruction (58).

5.5.2. MEASURING COPD OR ASTHMA

In epidemiological studies the outcome of disease/diagnoses is often assessed through a ‘gold standard test’ to minimise inclusion of differential diagnoses as cases. No ‘gold standard test’ is available to differentiate between COPD and asthma by spirometry. According to the ATS/ERS standardisation of lung function testing from 2005 there is no evidence to clearly differentiate asthma and COPD patients by bronchodilator response (57). The response to bronchodilators varies within and between individuals (81) and when predicted reference values were established as pre-bronchodilator values; this included some overestimation of the reversibility of a low FEV_1/FVC ratio. In the present study the differential diagnoses of asthma was managed in sensitivity analyses by excluding participants with self-reported prior asthma, although asthma and COPD may occur at the same time. Asthma predisposes to the development of COPD (82,83) and asthma is also associated to the investigated exposures (84,85) and is a potential confounder. Excluding asthmatics as defined from the analyses might underestimate the true association to occupation as an inclusion of the subjects is likely to overestimate the association. The best estimate might therefore be in-between these ORs. In Paper I the ORadj including and excluding asthmatics were very similar while we saw a non-significant increase of the estimates in Paper II-IV. This difference in the sensitivity analyses between Paper I and Paper II-IV might be due to smaller populations in Paper II-IV resulting in less stabile risk estimates. Thus the findings does not contradict that the best epidemiological estimate of COPD risk is in between calculated figures including and excluding asthma.

5.5.3. OCCUPATIONAL EXPOSURE ASSESSMENT

The occupational exposures were assessed by a self-administered questionnaire on exposures and occupation validated with an expert judgement. This approach is considered more sound than questionnaires alone (86), and our results support that the often used self-reported exposures might be prone to bias. This or similar combined approaches are well established and have been utilized in several population-based retrospective studies (61,77,87).

Recall bias of occupational exposure might be introduced tending to overestimate the association between exposure and disease. Although the risk was considered low, as the questionnaires were filled out before the GP examination, and thus only participants with well known COPD might have been more aware of job exposures. As patients with mild COPD have vague or no symptoms this assumption was tested by estimating the association of mild COPD and high organic dust exposure which slightly increased the ORadj (1.88 (95% CI: 1.13;3.13). This result supports that our findings unlikely are skewed by recall bias. Furthermore, few Danes aged 45 to 84 have knowledge of an association between occupational exposure to

VGDF and COPD, and the a priori selected DISCO-88 codes and expert management of each job title into DISCO-88, without awareness of COPD status, have further blinded the exposure assessment. As the prevalence of COPD was the same (p=0.63) among participants that have answered questions on work exposure and among those that did not, selection bias according to the exposure seems not to be a problem in the study. Furthermore, COPD was the main outcome of the planned study (51) and not related to the occupational exposure so this issue would probably not have reduced the initial response rate into the study.

The approach with four exposure categories is a simplified exposure assessment without consideration of all exposure details according to specific agents and exposure quantity. Misclassification of exposure can thus not be ruled out, but if introduced it would be non-differential. The main occupational exposure of organic dust may reflect the dominating position of agriculture in Northern Denmark as a special Danish occupational exposure scenario.

5.5.4. SMOKING EXPOSURE

In the personal assessment of smoking we found no common conversion of different types of smoking to the amount of cigarettes. We have applied the equations clinically used at Aalborg University Hospital, Denmark. This was nearly the same equation as Bernaards et al. used in their comparison study of calculating pack-years prospectively and retrospectively (88).

Passive smoke exposure was only considered as a confounder in Paper III among the never smokers. Only few never smokers had never experienced an exposure to passive smoke either at home or at work (n=45), probably due to the current age group and former smoking habits and behaviour among smokers in the society. Passive smoking was assessed as never/ever exposed and was not associated to COPD and additional adjustment for passive smoking changed only the estimates to a minor extent. This is in contrast to the study of never smokers by Hagstad et al. who found an association between passive smoking and COPD (89). They defined COPD according to the GOLD method and adjusted for socioeconomic status, based on occupation, but not a possible occupational exposure which might confound their estimates.

5.5.5. STRENGTHS AND LIMITATIONS

The external study validity is considered to be high in a Western world setting with similar occupational distribution, due to expected similar occupational exposures. However, the major contribution of organic dust exposure might reflect a special Danish occupational exposure scenario.

The overall enrolled study population included more young women and fewer participants in the oldest group than among non-responders. This might introduce an age dependent healthier study population tending to underestimate the associations. On the other hand, the included study population was older than populations from other articles in this research field (69,71,79) although some results are unexpected as the non-significant results of the annual FEV_1 and FVC decline.

Spirometry error measurements have been managed by regular calibration, but the variations of brands among GPP were neglected for the benefit of a local experienced operator. However, the internal biologically variability in lung function was addressed by requiring three sufficient measurements as recommended by the ERS and the ATS (57). Possible misclassifications of outcome would be of non-differential nature and tend to underestimate the associations. Some of the variability in between spirometer and operators was addressed by including the GPP as a random variable in the analyses. Moreover, when using a spirometrically-defined COPD some COPD patients with compliance difficulties might be excluded from the analyses possibly resulting in false low associations.

Information bias of exposure was probably reduced by using the specialist assessed exposure on the basis of job titles, instead of the commonly used self-reported exposure assessment. A validation of the self-reported exposures uncovered a large discrepancy between the occupational specialists and the participants regarding relevant exposures due to the stated job titles. The job titles often were connected to the wrong exposure and, furthermore, the specialists assessed many of the job titles as having no occupational exposure. As a consequence a significant discordance in the four exposure groups was observed comparing the dichotomised expert assessed exposure and the self-reported exposure in the unrestricted data set (N=4717). Furthermore, this was emphasised in the sub-analysis in Paper II where 24 women with a specialist defined tentative exposure were excluded and slightly increased the association.

6. CONCLUSION

Occupational VGDF and organic dust exposure were associated to COPD including analysis in subsets of non-smokers and females although a clear exposure-response relation was not observed in the longitudinal analysis. More detailed in:

Paper I We found in this population-based study involving 4697 subjects an age-standardised prevalence of COPD of 5.0%. Organic dust exposure was in a dose-dependent manner associated to the prevalence of COPD, independent of smoking habits, although the study found no associations to other less-common exposures.

Paper II We found in this population-based study involving 1626 women an age-standardised prevalence of COPD of 4.6%. Organic dust exposure was associated to the prevalence of COPD, independent of smoking habits. The population attributable fraction of occupational organic dust and COPD among women was 15%.

Paper III We found that occupational exposure to VGDF and organic dust significantly increased the risk of COPD corresponding to a high PAF (VGDF 48%) indicating that occupational exposures contributes substantial to the burden of COPD in never smokers. The major contribution of organic dust exposure among the VGDF exposures in this study might reflect a special Danish occupational exposure scenario.

Paper IV We found that occupational VGDF and organic dust exposure to increase the incidence of COPD, but without a clear exposure-response relation. However, the study found no statistical significant impact of occupational exposure on the annual declines in FEV_1 and FVC.

7. PERSPECTIVES

The present study emphasise the major influence that exposures from occupation as VGDF and organic dust have on COPD, also among never smokers and women. These findings from the labour market in Denmark might indicate that even low exposures from work over time can have an impact on the development of COPD. The awareness by recognising these data ought to be transformed to preventive efforts to eliminate occupational COPD and thus improve public health.

Included in the study, but not as a part of the Thesis is analysis involving selected candidate genes. By introducing this kind of analysis in occupational settings inborn susceptibility and gene-environment interaction can be studied. As genetic variations previously have shown some impact on COPD in different cohorts the genetic variation might influence the associations between occupational exposures and COPD. The intensity of the occupational exposure is generally less and of lower intensity compared to smoking. The genetic variants might therefore have another or more pronounced/clear impact on COPD when combined with occupational exposures than with smoking exposure.

The focus is upon candidate genes selected from studies in the oxidative defence, GWAS and well-known genetic associations as in alpha-1-antitrypsin deficiency.

We have included:

- 17 genes/areas corresponding to 32 single nucleotide polymorphisms (SNP) analysed by TaqMan OpenArray genotyping system from Applied Biosystems.
- Gene deletion - copy-number variation (CNV) in two genes analysed by quantitative polymerase chain reaction (qPCR).
- Number of repeats in one gene analysed by fragment analysis.

Finally the genetic results is planned to be replicated in another Danish cohort, but in younger persons.

8. REFERENCES

(1) Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD. 2014.

(2) Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095-2128.

(3) Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.

(4) Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2197-2223.

(5) Murray CJL. Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010). 2012; Available at: http://vizhub.healthdata.org/irank/heat.php. Accessed 12/18, 2013.

(6) Lokke A, Hilberg O, Tonnesen P, et al. Direct and indirect economic and health consequences of COPD in Denmark: a national register-based study: 1998-2010. BMJ Open 2014;4:e004069-2013-004069.

(7) Lokke A, Hilberg O, Kjellberg J, et al. Economic and health consequences of COPD patients and their spouses in Denmark--1998-2010. COPD 2014;11:237-246.

(8) Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005;26:319-338.

(9) Sherrill DL, Lebowitz MD, Knudson RJ, Burrows B. Continuous longitudinal regression equations for pulmonary function measures. Eur Respir J 1992;5:452-462.

(10) Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.

(11) Han MK, Agusti A, Calverley PM, et al. Chronic obstructive pulmonary disease phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182:598-604.

(12) Segreti A, Stirpe E, Rogliani P, Cazzola M. Defining phenotypes in COPD: an aid to personalized healthcare. Mol Diagn Ther 2014;18:381-388.

(13) Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007;370:741-750.

(14) Anto JM, Vermeire P, Vestbo J, Sunyer J. Epidemiology of chronic obstructive pulmonary disease. Eur Respir J 2001;17:982-994.

(15) Lokke A, Lange P, Scharling H, et al. Developing COPD: a 25 year follow up study of the general population. Thorax 2006;61:935-939.

(16) Wilson D, Adams R, Appleton S, Ruffin R. Difficulties identifying and targeting COPD and population-attributable risk of smoking for COPD: a population study. Chest 2005;128:2035-2042.

(17) Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009;374:733-743.

(18) Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet 2014.

(19) Tam A, Sin DD. Pathobiologic mechanisms of chronic obstructive pulmonary disease. Med Clin North Am 2012;96:681-698.

(20) Barker BL, Brightling CE. Phenotyping the heterogeneity of chronic obstructive pulmonary disease. Clin Sci 2013;124:371-387.

(21) Chambers DC, Gellatly SL, Hugenholtz P, Hansbro PM. JTD special edition 'Hot Topics in COPD'-The microbiome in COPD. J Thorac Dis 2014;6:1525-1531.

(22) Gomez-Mejiba SE, Zhai Z, Akram H, et al. Inhalation of environmental stressors & chronic inflammation: autoimmunity and neurodegeneration. Mutat Res 2009;674:62-72.

(23) MacNee W. Oxidative stress and lung inflammation in airways disease. Eur J Pharmacol 2001;429:195-207.

(24) Kukkonen MK, Tiili E, Vehmas T, et al. Association of genes of protease-antiprotease balance pathway to lung function and emphysema subtypes. BMC Pulm Med 2013;13:36-2466-13-36.

(25) Roca M, Verduri A, Corbetta L, et al. Mechanisms of acute exacerbation of respiratory symptoms in chronic obstructive pulmonary disease. Eur J Clin Invest 2013;43:510-521.

(26) Qureshi H, Sharafkhaneh A, Hanania NA. Chronic obstructive pulmonary disease exacerbations: latest evidence and clinical implications. Ther Adv Chronic Dis 2014;5:212-227.

(27) Hassett DJ, Borchers MT, Panos RJ. Chronic obstructive pulmonary disease (COPD): evaluation from clinical, immunological and bacterial pathogenesis perspectives. J Microbiol 2014;52:211-226.

(28) Postma DS, Kerkhof M, Boezen HM, Koppelman GH. Asthma and chronic obstructive pulmonary disease: common genes, common environments? Am J Respir Crit Care Med 2011;183:1588-1594.

(29) Kaneko Y, Yatagai Y, Yamada H, et al. The search for common pathways underlying asthma and COPD. International Journal of COPD 2013;8:65-78.

(30) Smolonska J, Koppelman GH, Wijmenga C, et al. Common genes underlying asthma and COPD? Genome-wide analysis on the Dutch hypothesis. Eur Respir J 2014;44:860-872.

(31) Wilk JB, Djousse L, Arnett DK, et al. Evidence for major genes influencing pulmonary function in the NHLBI family heart study. Genet Epidemiol 2000;19:81-94.

(32) Lieberman J, Winter B, Sastre A. Alpha 1-antitrypsin Pi-types in 965 COPD patients. Chest 1986;89:370-373.

(33) Dahl M, Tybjaerg-Hansen A, Lange P, et al. Change in lung function and morbidity from chronic obstructive pulmonary disease in alpha1-antitrypsin MZ heterozygotes: A longitudinal study of the general population. Ann Intern Med 2002;136:270-279.

(34) Bosse Y. Updates on the COPD gene list. International Journal of COPD 2012;7:607-631.

(35) Balmes J, Becklake M, Blanc P, et al. American Thoracic Society Statement: Occupational contribution to the burden of airway disease. Am J Respir Crit Care Med 2003;167:787-797.

(36) Ryu JY, Sunwoo YE, Lee SY, et al. Chronic Obstructive Pulmonary Disease (COPD) and Vapors, Gases, Dusts, or Fumes (VGDF): A Meta-analysis. COPD 2014.

(37) Oxman AD, Muir DC, Shannon HS, et al. Occupational dust exposure and chronic obstructive pulmonary disease. A systematic overview of the evidence. Am Rev Respir Dis 1993;148:38-48.

(38) Coggon D, Newman Taylor A. Coal mining and chronic obstructive pulmonary disease: a review of the evidence. Thorax 1998;53:398-407.

(39) Becklake MR. Chronic airflow limitation: its relationship to work in dusty occupations. Chest 1985;88:608-617.

(40) Becklake MR. Occupational exposures: evidence for a causal association with chronic obstructive pulmonary disease. Am Rev Respir Dis 1989;140:S85-91.

(41) Hendrick DJ. Occupational and chronic obstructive pulmonary disease (COPD). Thorax 1996;51:947-955.

(42) Burge PS. Occupation and COPD. Eur Respir Rev 2002;12:293-294.

(43) Viegi G, Di Pede C. Chronic obstructive lung diseases and occupational exposure. Curr Opin Allergy Clin Immunol 2002;2:115-121.

(44) Blanc PD, Torén K. Occupation in chronic obstructive pulmonary disease and chronic bronchitis: an update. Int J Tuberc Lung Dis 2007;11:251-257.

(45) The Norwegian Medical Association. Yrkesbetinget kronisk obstruktiv lungesykdom (KOLS) [Occupational COPD]. 2007.

(46) Cullinan P. Occupation and chronic obstructive pulmonary disease (COPD). Br Med Bull 2012;104:143-161.

(47) Omland O, Wurtz ET, Aasen TB, et al. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health 2014;40:19-35.

(48) Fell AK, Aasen TO, Kongerud J. Work-related COPD. Tidsskr Nor Laegeforen 2014;134:2158-2163.

(49) Hill AB. The Environment and Disease: Association Or Causation? Proc R Soc Med 1965;58:295-300.

(50) Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-19.

(51) Hansen JG, Pedersen L, Overvad K, et al. The Prevalence of chronic obstructive pulmonary disease among Danes aged 45-84 years: population-based study. COPD 2008;5:347-352.

(52) Lange P, Groth S, Nyboe J, et al. Chronic obstructive lung disease in Copenhagen: cross-sectional epidemiological aspects. J Intern Med 1989;226:25-32.

(53) Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5-40.

(54) American Thoracic Society. Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107-1136.

(55) Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012;40:1324-1343.

(56) The Global Lungs Function Initiative. 2013; Available at: http://www.lungfunction.org/.

(57) Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J 2005;26:948-968.

(58) Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. Eur Respir J 2014;43:505-512.

(59) Statistics Denmark. The Danish version of the International Standard of Occupations, version-88 (DISCO-88). Available at: http://www.dst.dk/da/Statistik/dokumentation/Nomenklaturer/DISCO-88.aspx. Accessed November 26, 2014.

(60) Rabe-Hesketh S, Skrondal A. Multilevel and Longitudinal Modeling Using Stata. 3rd ed. College Station, Texas: Stata Press; 2012.

(61) Bakke PS, Baste V, Hanoa R, Gulsvik A. Prevalence of obstructive lung disease in a general population: relation to occupational title and exposure to some airborne agents. Thorax 1991;46:863-870.

(62) Jaén Á, Zock JP, Kogevinas M, et al. Occupation, smoking, and chronic obstructive respiratory disorders: a cross sectional study in an industrial area of Catalonia, Spain. Environ Health 2006;5:2.

(63) Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2002;156:738-746.

(64) Kainu A, Rouhos A, Sovijarvi A, et al. COPD in Helsinki, Finland: socioeconomic status based on occupation has an important impact on prevalence. Scand J Public Health 2013;41:570-578.

(65) Melville AM, Pless-Mulloli T, Afolabi OA, Stenton SC. COPD prevalence and its association with occupational exposures in a general population. Eur Respir J 2010;36:488-493.

(66) Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Chest 2009;136:716-725.

(67) Lamprecht B, Schirnhofer L, Kaiser B, et al. Farming and the prevalence of non-reversible airways obstruction: results from a population-based study. Am J Ind Med 2007;50:421-426.

(68) Monsó E, Riu E, Radon K, et al. Chronic obstructive pulmonary disease in never-smoking animal farmers working inside confinement buildings. Am J Ind Med 2004;46:357-362.

(69) Mehta AJ, Miedinger D, Keidel D, et al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. Am J Respir Crit Care Med 2012;185:1292-1300.

(70) Halbert RJ, Natoli JL, Gano A, et al. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006;28:523-532.

(71) Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax 2005;60:645-651.

(72) Beck GJ, Schachter EN, Maunder LR, Schilling RS. A prospective study of chronic lung disease in cotton textile workers. Ann Intern Med 1982;97:645-651.

(73) Elwood PC, Sweetnam PM, Bevan C, Saunders MJ. Respiratory disability in ex-cotton workers. Br J Ind Med 1986;43:580-586.

(74) Eng A, 't Mannetje A, McLean D, et al. Gender differences in occupational exposure patterns. Occup Environ Med 2011;68:888-894.

(75) Sunyer J, Zock JP, Kromhout H, et al. Lung function decline, chronic bronchitis, and occupational exposures in young adults. Am J Respir Crit Care Med 2005;172:1139-1145.

(76) Blanc PD. Occupation and COPD: a brief review. J Asthma 2012;49:2-4.

(77) Weinmann S, Vollmer WM, Breen V, et al. COPD and occupational exposures: a case-control study. J Occup Environ Med 2008;50:561-569.

(78) Lam KB, Yin P, Jiang CQ, et al. Past dust and GAS/FUME exposure and COPD in Chinese: the Guangzhou Biobank Cohort Study. Respir Med 2012;106:1421-1428.

(79) Mirabelli MC, London SJ, Charles LE, et al. Occupation and three-year incidence of respiratory symptoms and lung function decline: the ARIC Study. Respir Res 2012;13:24-9921-13-24.

(80) Schermer TR, Quanjer PH. COPD screening in primary care: who is sick? Prim Care Respir J 2007;16:49-53.

(81) Johannessen A, Lehmann S, Omenaas ER, et al. Post-bronchodilator spirometry reference values in adults and implications for disease management. Am J Respir Crit Care Med 2006;173:1316-1325.

(82) Rasmussen F, Taylor DR, Flannery EM, et al. Risk factors for airway remodeling in asthma manifested by a low postbronchodilator FEV1/vital capacity ratio: a longitudinal population study from childhood to adulthood. Am J Respir Crit Care Med 2002;165:1480-1488.

(83) von Mutius E. Childhood experiences take away your breath as a young adult. Am J Respir Crit Care Med 2002;165:1467-1468.

(84) Toren K, Blanc PD. Asthma caused by occupational exposures is common - a systematic analysis of estimates of the population-attributable fraction. BMC Pulm Med 2009;9:7-2466-9-7.

(85) Lillienberg L, Andersson E, Janson C, et al. Occupational exposure and new-onset asthma in a population-based study in Northern Europe (RHINE). Ann Occup Hyg 2013;57:482-492.

(86) Teschke K, Olshan AF, Daniels JL, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. Occup Environ Med 2002;59:575-93; discussion 594.

(87) Blanc PD, Eisner MD, Earnest G, et al. Further exploration of the links between occupational exposure and chronic obstructive pulmonary disease. J Occup Environ Med 2009;51:804-810.

(88) Bernaards CM, Twisk JW, Snel J, et al. Is calculating pack-years retrospectively a valid method to estimate life-time tobacco smoking? A comparison between prospectively calculated pack-years and retrospectively calculated pack-years. Addiction 2001;96:1653-1661.

(89) Hagstad S, Bjerg A, Ekerljung L, et al. Passive Smoking Exposure Is Associated With Increased Risk of COPD in Never Smokers. Chest 2014;145:1298-1304.

9. APPENDICES

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APPENDIX A. BASELINE DATA ESTABLISHMENT - 2004 (DANISH)

Baseline data source from the GP examination and the participant self-administered questionnaire.

PATIENT NO.:

Lægeskema

Dato: ________________________

Patientinitialer: ________________

CPR nummer: _________________

BT: _________________________

Vægt: _______________________

Højde: _______________________

Taljeomkreds: _________________

Hofteomkreds: ________________

Blodprøve udtaget: Ja: Label påklæbes her

Nej: Angiv årsag: ______________________

Dette skema vedlagt resultat af spirometrien, patientskemaerne og underskrevet samtykkeerklæring (husk at patienten skal have en kopi) sendes til projektledelsen i den frankerede svarkuvert

Send blodprøven med label til Laboratoriet for Stamcelleforskning i den frankerede svarkuvert

Tak for hjælpen

Projektledelsen
21. september 2004

Kronisk obstruktiv lungesygdom i Nordjylland og Viborg Amter, Aalborg Sygehus, Århus Universitetshospital, Stengade 10,2 9000 Aalborg.

PATIENT NO.:

Medicinske oplysninger

Sæt venligst kryds ud for hvert spørgsmål:

Lider De af eller har De lidt af følgende sygdomme? (sæt kryds)

a. Blodprop i hjertet ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang ______

b. Hjertekrampe (angina pectoris) ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang ______

c. Anden form for hjertesvækkelse ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang ______

d. Forhøjet blodtryk ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang ______

e. Lungekræft ☐ Nej ☐ Ja

Hvis "ja", hvor gammel var De da sygdommen optrådte første gang ______

f. Er De blevet opereret for lungekræft? ☐ Nej ☐ Ja

Hvis ja, hvor gammel var De? ______

g. Andre kræftsygdomme ☐ Nej ☐ Ja

Hvis "ja", hvilken ______

PATIENT NO.:

Familieoplysninger

1. Er der hos Deres biologiske **mor** på noget tidspunkt konstateret følgende sygdomme:

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:______

2. Er der hos Deres biologiske **far** på noget tidspunkt konstateret følgende sygdomme:

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:______

3. Er der hos Deres biologiske **søskende** på noget tidspunkt konstateret følgende sygdomme

(sæt kryds)

a. Astma ☐ Nej ☐ Ja ☐ ved ikke

b. Kronisk obstruktiv lungesygdom (KOL) – også kaldet kronisk bronchitis eller for store lunger? ☐ Nej ☐ Ja ☐ ved ikke

c. Andre lungesygdomme? ☐ Nej ☐ Ja ☐ ved ikke

Hvis "ja", angiv hvilken sygdom det drejer sig om:______

PATIENT NO.:

Uddannelse og arbejde

Uddannelse

1. Hvor mange år har De gået i skole?

(sæt kryds)

- 1 1. 7 år eller mindre (folkeskole) ☐
- 1.2. 8-10 år (mellemskole, realeksamen) ☐
- 1.3. Over 10 år (præliminæreksamen, studentereksamen) ☐

2. Hvilken videregående uddannelse har De fået efter endt skolegang?
Vi er interesserede I uddannelsens længde, uanset om den var boglig eller praktisk.
(Hvis De har gennemgået flere uddannelser, skal De markere ved den længstvarende uddannelse)

(sæt kryds)

- 2.1 Ingen erhvervsuddannelse ☐
- 2.2 Kort videregående uddannelse, under 3 år ☐
- 2.3 Mellemlang videregående uddannelse, 3-4 år ☐
- 2.4. Lang videregående uddannelse, over 4 år ☐

Opvækst

(sæt kryds)

3.1. Er De opvokst på en gård? ☐ Nej ☐ Ja

Hvis ja
3.2. Var der husdyr på gården ☐ Nej ☐ Ja

Arbejde (hele dit arbejdsliv)

	≥20 år	19-15 år	14-10 år	9-5 år	≤ 5 år	slet ikke
4.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for støv fra planter (f.eks. halm eller træstøv) eller dyr?	☐	☐	☐	☐	☐	☐
4.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. landmand)						
Angiv max. de tre længst varende						
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐

	≥20 år	19-15 år	14-10 år	9-5 år	< 5 år	slet ikke
5.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for støv fra cement, granit, nedrivninger eller lignende?	☐	☐	☐	☐	☐	☐
5.2 Hvis De var udsat hvad var jobbet/ jobbene? (f.eks. murer)						
Angiv max. de tre længst varende						
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
6.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for røg fra smeltet metal eller svejsning?	☐	☐	☐	☐	☐	☐
6.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. svejser)						
Angiv max. de tre længst varende						
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
7.1 Hvor længe har De sammenlagt i Deres arbejde (ikke nødvendigvis i et stræk) været udsat for dampe fra malinger eller lime?	☐	☐	☐	☐	☐	☐
7.2 Hvis De var udsat, hvad var jobbet/ jobbene? (f.eks. sprøjtemaler)						
Angiv max. de tre længst varende						
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐
______________________	☐	☐	☐	☐	☐	☐

PATIENT NO.:

Rygevaner

1. Har De nogensinde røget cigaretter, cerutter, cigarer eller pibe regelmæssig, dvs. Mindst en cigaret, cerut, cigar eller et pibestop dagligt gennem et år

☐ **Nej** ☐ **Ja** **Hvis "nej", gå til side 2 "passiv rygning" (spørgsmål 11, 12 og 13)**

2. Ryger De dagligt for tiden

☐ **Nej** ☐ **Ja** **Hvis "nej", gå til "tidligere rygning"**

Nuværende rygning

3. Hvor meget ryger De dagligt? (Hvis der er tobakstyper, De ikke ryger, svares 0)

Antal	**1-5**	**6-10**	**11-15**	**16-20**	**≥ 21**
a. Antal cigaretter	☐	☐	☐	☐	☐
b. Antal cerutter	☐	☐	☐	☐	☐
c. Antal cigarer	☐	☐	☐	☐	☐
d. Antal pibestop	☐	☐	☐	☐	☐

4. Hvilken type cigaretter ryger De?
   e. Mest med filter ☐
   f. Mest uden filter ☐
   g. Både med og uden filter ☐

5. Inhalerer De tobaksrøgen, når De ryger? (sæt en markering for hver tobakstype)

	Nej, inhalerer aldrig	Ja, lidt	Ja, dybt
h. Cigaretter	☐	☐	☐
i. Cerutter	☐	☐	☐
j. Cigarer	☐	☐	☐
k. Pibe	☐	☐	☐

Tidligere rygning

6. Hvor gammel var De, da De begyndte at ryge dagligt? ______ år

7. Hvor mange år har De i alt røget dagligt? ______ år

8. Hvor gammel var De, da De holdt op? ______ år

9. Har der siden De begyndte at ryge og inden De eventuelt holdt op sidste gang, været perioder på mere end et år, hvor De ikke har røget?

☐ Nej ☐ Ja

Hvis "ja", bedes De angive de perioder af Deres liv, hvor De ikke har røget
Fra alder ____år Til alder ____år
Fra alder ____år Til alder ____år
Fra alder ____år Til alder ____år

Kronisk obstruktiv lungesygdom I Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

10. Hvor meget røg De dagligt, da De var I følgende aldersgrupper? (hvis der er tobakstyper, De ikke har røget, svares "0")

20-29 år	Antal
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pbestop	
30-39 år	
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pibestop	
40-49 år	
Cigaretter med filter	
Cigaretter uden filter	
Cigaretter med/uden filter	
Cerutter	
Cigarer	
Pibestop	

Passiv rygning

11. Blev der røget I Deres barndomshjem?

Deres alder	**Ingen i husstanden røg**	**Én eller flere i husstanden røg**
0-9 år	☐	☐
10-19 år	☐	☐

12. Blev der røget I Deres hjem i følgende perioder af Deres liv?

Deres alder	**Ingen i husstanden røg**	**Én eller flere i husstanden røg**
20-29 år	☐	☐
30-39 år	☐	☐
40-49 år	☐	☐
50 år og indtil nu	☐	☐

13. Hvor mange timer om dagen har De gennemsnit været udsat for andres tobaksrøg på Deres arbejde I følgende perioder af Deres liv?

Deres alder	**Arbejdede ikke udenfor hjemmet**	**Antal timer udsat for andres tobaksrøg**			
		0	**1-3**	**4-7**	**8 el. flere**
Under 20 år					
20-29 år					
30-39 år					
40-49 år					
50 år indtil nu					

Kronisk obstruktiv lungesygdom I Nordjyllands og Viborg Amter. Aalborg Sygehus, Aarhus Universitetshospital, Stengade 10,2 9000 Aalborg

PATIENT NO.:

Alkoholvaner

1. Hvor gammel var De, da De begyndte at drikke én eller flere genstande alkohol (øl, vin, hedvin eller spiritus) om måneden? (sæt kryds)

Har aldrig drukket over én genstand pr. måned	Mindre end 14 år	14-16 år	17-18 år	19-20 år	21-25 år	Over 25 år

Nuværende alkoholforbrug

2. Hvor ofte drikker De almindeligvis alkohol (øl, vin, hedvin eller spiritus)?

   a. Drikker ikke øl, vin, hedvin eller spiritus ☐ (sæt kryds)
   b. Mindre end 1 gang om måneden ☐
   c. 1-3 gange om måneden ☐
   d. 1 gang om ugen ☐
   e. 2-4 gange om ugen ☐
   f. 5-6 gange om ugen ☐
   g. Hver dag ☐

Tidligere alkoholforbrug

De følgende spørgsmål skal belyse ændringer i Deres alkoholforbrug.

3. Hvor mange genstande (øl, vin, hedvin, eller spiritus) drak De almindeligvis om ugen, da De var I følgende aldersgrupper?
   Hvis der er typer af alkohol, De ikke har drukket, svares 0

Alder	Øl, ca.	Vin, ca.	Hedvin, ca.	Spiritus, ca.
20-29 år				
30-39 år				
40-49 år				
50 år indtil nu				

4. Har der, siden De begyndte at drikke alkohol været perioder på mere end et år, hvor De ikke har drukket alkohol?
   ☐ Nej ☐ Ja

Hvis ja, bedes De angive de perioder af Deres liv, hvor De ikke har drukket alkohol?

Periode	Fra alder	Til alder
1		
2		
3		

PATIENT NO.:

Astma og allergi

(Sæt kryds)

1. Har De nogensinde haft astma ? ☐ Nej ☐ Ja
2. Var dette bekræftet af læge? ☐ Nej ☐ Ja
3. Har De allergi i øjne eller næse (høfeber)? ☐ Nej ☐ Ja
4. Hoster De eller har De af og til problemer med vejrtrækningen om natten? ☐ Nej ☐ Ja
5. Har De af og til anfald med åndenød eller piben/hvæsen uden at have anstrengt Dem? ☐ Nej ☐ Ja
6. Hoster De I flere uger efter en almindelig forkølelse? ☐ Nej ☐ Ja
7. Får De astmamedicin, som hjælper godt på Deres gener? ☐ Nej ☐ Ja

APPENDIX B. FOLLOW-UP DATA ESTABLISHMENT - 2008 (DANISH)

Follow-up data source from the GP examination and the participant self-administered questionnaire.

Lægeskema til KOL follow-up undersøgelse 2008.

Patientnummer: fortrykt.

Navn og CPR nummer:

Dato:

Højde:

Vægt:

Hoftemål:

Taljemål:

BT:

Resultat af spirometri:

Dette skema sendes sammen spirometrimålingen, spørgeskema, og samtykkeerklæringen til projektledelsen i vedlagte frankerede svarkuvert. Tak for hjælpen

Patientnummer: fortrykt

Sådan udfyldes skemaet

Inden De besvarer spørgsmålene, bedes De læse både spørgsmål og svar igennem.
Spørgsmålene besvares ved at sætte kryds i den kasse, hvor De synes, svaret passer bedst.
Sæt kun ét kryds ved hvert spørgsmål, medmindre andet er angivet.

Lungesygdomme

Nedenfor følger en række spørgsmål, hvorvidt De har haft lungesygdomme, siden De deltog i den første lungeundersøgelse.

1. Har De haft anfald af akut bronkitis siden De deltog i den første lungeundersøgelse?

Ja.................. ☐
Nej .... ☐ gå venligst til spørgsmål 5
Ved ikke ....☐ gå venligst til spørgsmål 5

2. Angiv hvor mange anfald, De har haft

Antal anfald ______________________

3. Blev Deres akutte bronkitis bekræftet af en læge?

Ja.................. ☐
Nej .... ☐
Ved ikke ....☐

4. Hvilken behandling har De modtaget for akut bronkitis?

(Gerne flere kryds)
Astmamedicin...........................☐
Penicillin ....☐
Anden medicin ....☐ angiv venligst hvilken ____________________
Anden behandling ....☐ angiv venligst hvilken ____________________

5. Har De haft lungebetændelse siden De deltog i den første lungeundersøgelse?

Ja.................. ☐
Nej .... ☐ gå venligst til spørgsmål 9
Ved ikke ....☐ gå venligst til spørgsmål 9

6. Angiv hvor mange gange, De har haft lungebetændelse

Antal lungebetændelser __________________

7. Blev Deres lungebetændelse bekræftet af en læge?

Ja.................. ☐
Nej .... ☐
Ved ikke ....☐

8. Hvilken behandling har De modtaget for lungebetændelse?

(Gerne flere kryds)
Astmamedicin...........................☐
Penicillin ....☐
Anden medicin ....☐ angiv venligst hvilken ____________________
Anden behandling ....☐ angiv venligst hvilken ____________________

9. Har De haft astmaanfald siden De deltog i den første lungeundersøgelse?

Ja.................. ☐
Nej .... ☐ gå venligst til spørgsmål 13
Ved ikke ....☐ gå venligst til spørgsmål 13

10. Angiv hvor mange gange, De har haft astmaanfald

Antal anfald __________________

11. Blev Deres astmaanfald bekræftet af en læge?

Ja.................. ☐
Nogle anfald ......☐
Nej .... ☐
Ved ikke ....☐

12. Hvilken behandling har De modtaget for astma?

(Gerne flere kryds)
Astmamedicin...........................☐
Penicillin ....☐
Anden medicin ....☐ angiv venligst hvilken ____________________
Anden behandling ....☐ angiv venligst hvilken ____________________

Rygning

Nedenfor følger en række spørgsmål om rygning.

13. Ryger De?
Ja.................. ☐
Nej .... ☐ gå venligst til spørgsmål 15

14. Hvor meget ryger De sædvanligvis om dagen? Angiv Deres rygning nedenfor. Gå derefter direkte til spørgsmål 16.

(Antal pr dag)
Cigaretter, antal: ________________
Cigarer, antal: ________________
Cerutter, antal: ________________
Pibetobak, antal stop: ________________

15. Har De tidligere røget?

Ja, men jeg ryger ikke længere.................. ☐ angiv venligst årstal for hvornår De er ophørt _______________

Nej .... ☐ gå venligst til spørgsmål 17

16. Har De forsøgt rygestop?

Nej .... ☐
Ja, enkelte gange ☐
Ja, adskillige gange ☐

Alkoholbrug

Nedenfor følger en række spørgsmål om alkoholbrug.

17. Drikker De alkohol?

Ja ....☐
Nej .... ☐ gå venligst til spørgsmål 19

18. Hvor meget alkohol drikker De sædvanligvis på en uge? Angiv venligst Deres alkoholbrug i skemaet nedenfor. Gå derefter direkte til spørgsmål 20.

	(Antal genstande pr uge)
Øl antal	________
Vin, antal	________
Hedvin, antal	________
Spiritus, antal	________

19. Har De nogensinde drukket alkohol?

Nej ....☐
Ja, men jeg er stoppet med at drikke alkohol ☐
Angiv venligst årstal for, hvornår De er stoppet: _________

Arbejde

Nedenfor følger en række spørgsmål om Deres arbejdssituation, siden De deltog i den første lungeundersøgelse.

20. Er der ændringer med hensyn til Deres arbejde siden De deltog i den første lungeundersøgelse?

Ja .... ☐
Nej .... ☐ gå venligst til afslutning af skemaet

21. Hvornår har ændringerne fundet sted?

Årstal _________

22. Hvilke ændringer er der sket?

Jeg er ophørt med at arbejde .... ☐ gå venligst til spørgsmål 23
Jeg er gået ned i arbejdstid .... ☐ gå venligst til spørgsmål 23
Jeg har skiftet job .... ☐ gå venligst til afslutning af skemaet
Jeg er gået op i arbejdstid .... ☐ gå venligst til afslutning af skemaet
Andre ændringer .... ☐ angiv venligst hvilke ____________

23. Hvorfor er disse ændringer i Deres arbejdssituation sket?

Jeg er blevet pensioneret pga. alder ....☐
Jeg er blevet pensioneret pga. sygdom .... ☐ angiv venligst sygdom __________
Jeg er gået på efterløn ....☐
Jeg er blevet afskediget .... ☐
Jeg har sagt mit arbejde op .... ☐
Andre årsager ....☐angiv venligst årsag ____________

De er velkommen til at uddybe Deres svar nedenfor. Angiv venligst numrene på de spørgsmål, De uddyber.

____
____
____
____
____
____
____
____
____
____
____
____

Vær venlig at kigge spørgeskemaet igennem for at se, om alle spørgsmål er besvaret og medbring spørgeskemaerne til undersøgelsen hos Deres læge.

MANGE TAK FOR HJÆLPEN.

APPENDIX C. SELECTED DISCO-88 CODES (DANISH)

Indtastningsmanual for spørgsmål vedr. arbejde for projektet KOL i Nordjylland og Viborg Amt

Projektleder Jens Georg Hansen

Manualen er udarbejdet af Vivi Schlünssen og Øyvind Omland. Stillingsbeskrivelser med eksponering for støv, gasser og dampe er valgt efter uafhængig score fra begge. De stillingsbeskrivelser, hvor der har været overensstemmelse er medtaget uden yderligere diskussion. Hvor der ikke har været overensstemmelse, er nogle medtaget efter en uddybende diskussion. Selve kodningen er udarbejdet på basis af Danmarks Statistiks DISCO-88, timbuktu.dst.dk/internet/NOMEN/DISCO/DISCO887.htm og Discoløn 2004, 4. udgave, Danmarks Statistik december 2003, ISBN 87-501-1366-6.

I alt er der udvalgt 72 koder for stillingsbeskrivelser, hvor det vurderes, at arbejdet kan medføre en eksponering for støv, gasser og dampe, der i karakter, intensitet og varighed kan betegnes som en mulig årsagsfaktor til KOL. Vurderingen har taget højde for ændringer i eksponeringsniveauer og har lagt vægt på historiske eksponeringsniveauer, relevant for den aktuelle alderssammensætning, for de stillingsbetegnelser, hvor der har fundet en eksponeringsreduktion sted over tid. I alt er der beskrevet 34 stillingsbeskrivelser for organisk støv, 21 for uorganisk støv, 7 for både uorganisk støv og røg, 5 for damp, 3 for røg og 2 for både organisk og uorganisk støv. Koderne ligger fra 1311 til 9330. For andre stillingsbetegnelser end dem, der er anført i manualen, foreslås anvendt 9999. Hovedparten af disse stillingsbeskrivelser ligger indenfor områderne: Ledelse (1xxx), forskning og anvendelse af færdigheder på højeste niveau inklusive undervisning (2xxx), arbejde, der forudsætter færdigheder på mellemniveau (3xxx), kontorarbejde (4xxx), salgs-, service- og omsorgsarbejde (5xxx), og militært arbejde (0xxx). Der er medtaget 8 stillingsbetegnelser indenfor disse områder (4 indenfor 1xxx, 2 indenfor 2xxx, 1 indenfor 3xxx, 1 indenfor 5xxx). De øvrige 64 findes indenfor arbejde med landbrug, gartneri, skovbrug, jagt og fiskeri (6xxx), håndværkspræget arbejde (7xxx), proces- og maskinoperatørarbejde samt transport- og anlægsarbejde (8xxx) og andet arbejde (9xxx).

Indtastningen for erhvervsspørgsmålene foreslås udført som for de øvrige spørgsmål i skemaet. De besvarelser, hvor der er usikkerhed i kodningen lægges til side og gennemgås ugentligt af en arbejdsmediciner (Vivi Schlünssen, Svend Viskum eller Øyvind Omland) med henblik på endelig kodning. Denne gennemgang og kodning kan udføres i samarbejde med Jens Georg Hansen i den udstrækning, han ønsker det. De kodede skemaer lægges til projektets sekretær til indtastning.

Århus, den 19.10.2004, Øyvind Omland

13	***Ledelse af virksomheder med færre end ti ansatte***
1311	Gård- og planteskolebestyrer (o)
1312	Bageribestyrer og systueindehaver (o)
1313	Bygmester (o)
1318	Renseriejer (d)
22	***Forskning og/eller anvendels af færdigheder indenfor medicin, farmaci og de biologiske grene af naturvidenskab.***
2213	Hortonom, landbrugskandidat, planteavlskonsulent (o)
2223	Dyrlæge (o)
322	***Assistentarbejde indenfor sundhedssektoren***
3227	Kennelassistent, veterinærsygeplejerske (o)
516	***Overvågnings- og redningsarbejde***
5161	Brandmand, røgdykker (r)
611	***Arbejde vedrørende plantevækst***
6111	Markarbejder i landbruget (o)
612	***Arbejde med dyr***
6121	Staldarbejder i landbruget (o)
6122	Fjerkræavler, ægproducent (o)
6129	Minkfarmer (o)
613	***Arbejde med såvel markafgrøder som husdyr***
6130	Landmand, landbrugsmedhjælper (o)
614	***Arbejde indenfor skovbrug***
6141	Skovløber, plantør (o)
711	***Mine- og stenhuggerarbejde***
7111	Minearbejder (u)
7113	Stenhugger (u)
712	***Bygningsarbejde (basis)***
7121	Tagtækker (u)
7122	Murer, flisemester (u)
7123	Terrassoarbejder, struktør (u)
7124	Tømrer, snedker, bådebygger (o)
713	***Bygningsarbejde (finish)***
7131	Tagdækker (u)
7132	Gulvafhøvler, gulvlægger (o)
7133	Stukkatør (u)
7134	Isolatør (u)
714	***Maler, tapetsererarbejde m.v.***
7141	Maler, skibsmaler, skiltemaler (d)
7142	Sprøjte-, autolakerer (d)
7143	Skorstensfejer (o)

72	***Metal- og maskinarbejde***
7211	Former, Støber (u)
7212	Svejser (r)
7213	Karosseribygger, kedel-, kobber-, pladesmed (u, r)
7214	Skibsbygger, stålmester (u, r)
7215	Rigger (u, r)
722	***Grovsmede-, værktøjsmagerarbejde***
7224	Metalsliber (u)
741	***Arbejde indenfor nærings- og nydelsesmiddelindustrien***
7411	Røgemester (r)
7412	Bager (o)
7416	Cigarmager, tobakssorterer (o)
742	***Arbejde indenfor træindustrien***
7421	Træimprægneringsarbejder (o)
7423	Maskindrejer, trædrejer (o)
811	***Mine- og mineraludvindingsanlægsarbejde***
8111	Borer (u)
8112	Mineral- og stenbrudsanlægsarbejder (u)
8113	Driller, borepladsarbejder (u)
812	***Jern-, metalværkds- og støberianlægsarebjde***
8121	Stålarbejder (u, r)
8122	Smelter (u, r)
8123	Støberiarbejder (u, r)
813	***Glas-, keramik- og teglprocesanlægsarbejde***
8131	Ovnarbejder, teglværksarbejder (u, r)
814	***Træ- og papirprocesanlægsarbejde***
8141	Finerarbejder, savskærer (o)
8143	Papirarbejder (o)
815	***Kemisk procesanlægsarbejde***
8151	Elementstøber, knusemester (u)
8152	Lakkoger (d)
821	***Betjening af maskiner indenfor metal- og mineralindustrien***
8212	Betonblander, cementarbejder (u)
822	***Betjening af maskiner indenfor den kemiske industri***
8222	Ammunitionsarbejder (u)
8223	Industrilakerer (d)
824	***Betjening af maskiner indenfor træindustrien***
8240	Savværksarbejder, træarbejder (o)

825	***Betjening af maskiner indenfor den grafiske industri og papirvareindustrien***
8252	Bogbinderassistent (o)
8253	Papirvarearbejder, æskearbejder (o)
826	***Betjening af maskiner indenfor tekstil-, skind- og lædervareindustrien***
8261	Karter, spinder, spoler (o)
827	***Betjening af maskiner indenfor nærings- og nydelsesmiddelindustrien***
8273	Møller, mølleriarbejder (o)
8274	Bageriarbejder, bageriassistent (o)
8276	Sukkerarbejder (o)
8277	Kaffebrænder (o)
8279	Cigaretarbejder, skråtobaksspinder (o)
828	***Monterings- og samlebåndsarbejde***
8285	Finersamler, møbelbehandler (o)
833	***Arbejde med andre mobile maskiner og køretøjer***
8331	Traktorfører (o, u)
8332	Maskinfører, gravemester (o, u)
916	***Renovations- og gadefejerarbejde***
9161	Renovationsarbejder (o)
9162	Gadefejer (u)
92	***Medhjælp indenfor landbrug, gartneri, fiskeri og skovbrug***
9211	Landbrugs- og gartnerimedhjælper (o)
9212	Skovhugger, plantagearbejder (o)
931	***Manuelt arbejde indenfor bygge- og anlægssektoren***
9311	Grusgravarbejder (u)
9312	Asfaltarbejder, vejarbejder (u, d, r)
9313	Murerarbejdsmand, bygningsarbejder (u)
933	***Manuel transport- og lagerarbejde***
9330	Havnearbejder, lagerarbejder og læssemand (u)

o = organisk støv
u = uorganisk støv
r = røg
d = damp

APPENDIX D. APPLIED DISCO-88 CODES AND CORRESPONDING OCCUPATIONAL ANSWERS (DANISH)

APPENDIX D.1: DISCO-88 koder indenfor organisk støv (org) eksponering

Koder	• **Udvalgte koder: 34 (org), 2 (org + inorg)** • **Anvendte koder: 27 (org) – se nedenfor** • **Ikke anvendte koder:** • **7 (org): 1312, 7132, 7421, 8141, 8252, 8274, 8276** • **2 (org + inorg): 8331, 8332**

DISCO	Spørgeskema tekst
1311	• Planteskoleejer • Selvstændig gartneriejer • Selvstændig: frugt, grønt, blomster
1313	• Bygmester • Entreprenør, formand • Tilsynsførende på byggepladser • Tømrer – byggemester
2213	• Landbrugsuddannelse, konsulent (frøavl) • Svinekonsulent • Zoologisk konservator
2223	• Dyrlæge • Embedsdyrlæge • Praktiserende dyrlæge
3227	• Dyrehandel • Hundepension
6111	• (Landbrug) – gartneri • Anlægsgartner • Arbejdsmand – gødningsstøv • Frugtavler • Gartner • Gartner, jernvare, møbelfabrik (også kodet: svejser, sprøjtemaler) • Gartneri • Gartneri medhjælper • Gartneri, landbrug • Gartneriuddannelse • Halm • Halm, træstøv • Halmvarmeværk-fliseværk • Kabelgravning • Kartoffelsorterer • Køre halm ind + fyre med halm 3-5 gange daglig • Landmand-traktorfører • Maskinstation • Medarbejdende hustru i planteskole • Medhjælp i gartneri • Meje ved landbrug • Mejetærskefører • Planteskole • Planteskolegartner • Støv fra halm • Ufaglært gartner • Varmemester (brændsel-halm)
6121	• 1 år som medhjælp i stald • 200+ privat dyr/fuglehold • Arbejde i svinestald • Arbejder med heste • Dyr • Dyr – grise, heste • Dyr, halm

	• Dyr, halm, høstøv • Halm, dyr • Halm, hø, ridelærer, foderstoffer • Halm, korn, køer, grise • Halm, træstøv, dyr • Hesteavl • Hesteopdræt • Hestepasser • Hestestald • Hjalp til i stalden • Husdyr • Inseminør • Kostaldmedhjælper • Kreatur • Kvæg, svin, halm • Køer og svin • Landbrug m husdyr • Landmand - haft hest • Landmand med kvæg • Medhjælper i stald • Opvokset på gård, i stald, egen gård med dyr • Svin • Svineavl • Svinefodermester • Svinestald • Svinestald som svinefodermester/ driftsleder
6122	• Hønsefarm • Hønseri • Kyllingefarm • Kyllinger • Pasning af fjerkræ
6129	• Medhjælp i minkfarm • Mink • Mink i fritiden • Minkavler • Minkfarm • Pelsdyr • Pelsdyravler • Pelsdyravler, træstøv 1 mdr årlig i 53 år

6130	• Arbejde på ægtefælles gård • Arbejdet og boet på en gård • Arbejdet på gården • Boede og arbejde i fritiden på et husmandssted • Bonde • Deltaget i landbrug hele livet • Deltidslandmand • Fodermester • Foderstof og landbrug • Folkeskolelærer/hobby landmand • Fritidslandmand • Fåreavler • Gedefarm • Hobbylandbrug • Landbrug • Landbruget • Landbrugsdrift • Landbrugsmedhjælper, hustru • Landmand • Landmand – delvis • Landmand + rengøring • Landmand og minkavler • Landmand, arbejdsmand, murer, sømand, lastbilchauffør • Landmand, chauffør, lagermand • Landmand, chauffør, reder • Landmand, chauffør, slagteriarbejder • Landmand, gartner • Landmand, graver • Landmand, grønttørreri • Landmand, industri træ • Landmand, kommunalarbejder

	• Landmand, maskin…, teglværk • Landmand, maskinstation • Landmand, mekaniker • Landmand, savskærer, buschauffør • Landmand, savværksarbejde • Landmand, specialarbejder på træ/møbelfabrik • Landmand, svin og slagte kyllinger • Landmand, traktorfører • Landmand, tømrer-bygningsarbejder • Landmand, vicevært • Landmand, vognmand (dyr, briketter) • Lidt landbrug • Maskinstation/landbrug • Medhjælpende hustru i landbrug • Medhjælpende hustru på gård • Medhjælpende hustru til landmand • Medhjælper landbrug, gift med landmand • Selvstændig landmand
6141	• Skovbrug • Skovbruger
7124	• Bygningssnedker / tømrer • Forskallingstømrer • I lære som snedker • Læretid som tømrer • Møbelsnedker • Skibssnedker • Skibstømrer • Snedker • Snedker (møbel) • Snedker/lakerer

	• Snedker/møbelfabrikant • Snedkeri • Træstøv - tømrer/snedker • Træstøv under mesterlære som karetmager/tømrer • Tømrer • Tømrer (byggeplads, værksted) • Tømrer asbestplader • Tømrer samt skibstømrer • Tømrer/bygningsarbejder • Tømrer/snedker • Tømrerlærling • Tømrersvend • Tømrervirksomhed • Tømrerværksted
7143	• Skorstensfejer
7412	• Bager • Bager (melstøv) • Bagerkone • Bageri • Bagersvend • Mel • Pakkeri brødfabrik
7416	• Cigarmager/ snusblanding
7423	• Bødker
8143	• Papirmølle
8240	• Arbejde på spånpladefabrik • Brændselarbejder • Højtaler – støv fra finer og spånplader • Maskinsnedker • Møbelfabrik • Møbelfabriksarbejder • Møbelindustriarbejder • Møbelindustrien • Møbel-maskinsnedkeri • Møbelproduktion • Savfører • Savskærer

	• Savværk • Savværk, trævarefabrik, plast, smedeværksted • Savværksarbejder • Specialarbejder i træindustri (pudse-/slibearbejde) • Træfabrik • Træindustri • Træindustri lager og chauffør • Træindustri lak-lim • Træstøv • Trævarefabrik • Tømrer arbejder på en køkkenfabrik
8253	• Bates ventil sække, Nørresundby • Kartonnage
8261	• Arbejde med huder og skind • Buntmager • Dynefabrik, fjer • Fabrik - syerske • Fabrik konfektion • Fiberstøv fra tøj • Konfektionsindustri • Lædervarefabrik - tilskærer • Modist • Møbelpolster • Møbelpolstring, hund • Rebslageri • Syerske • Systue • Sækkefabrik • Tekstilarbejde • Tekstilfabrik • Tekstilforædling • Tekstilindustri • Tekstilmedarbejder • Tilskærer • Væver
8273	• …foderstof

	• …formaling af korn og mel • Foderfabrik • Foderstof • Foderstof, mølleri • Foderstoffabrik • Foderstoffer • Foderstoffirma • Frørenseri • Korn • Korn og foderstoffer • Kornbehandlingsanlæg • Kornfoderfirma • Kornlager • Kornstøv • Korntørreri • Lagerarbejde korn/foderstof • Lagerarbejder (foderstof) • Lagermand – korn • Læreplads med foderstof og brændsel • Lærling korn og foderstoffer • Mølleri • Mølleri – korn og mel • På mølle (kornstøv) • Solsikkeskrå, pakhuse foderstof • Svinefoder
8277	• Kaffe – rå
8279	• Cigarmager • CV Obel • Skandinavisk tobak • Tobaksarbejde • Tobaksfabrik • Tobaksstøv • Tobaksstøv, maskinarbejder
8285	• Træ/finer
9161	• Renovationsarbejder
9211	• Alt-mulig-mand på gård • Ansat på en gård • Arbejde for bønder

	• Arbejdede på gårde, kvæghaller, kornmagasiner • Arbejdet med landbrug • Arbejdet på landet • Arbejdsmand på gård • Boet og arbejdet på gård • Gårdskarl • Hjalp i landbruget • Hjalp på gården • Hjalp til på en gård • Hjalp til på gården • Karl på gård • Landarbejder • Landbrug hos forældre (22-27 + 33-40 år) • Landbrug/maskinstation • Landbrugsarbejder • Landbrugselev • Landbrugsmedarbejder og gartneriarbejder • Landbrugsmedarbejder, fodermester • Landbrugsmedhjælper • Landmand, arbejdsmand • Landmandsarbejde • Landmandselev • Markarbejde, arbejde i svinestald • Maskinarbejde, passet køer, passet grise • Medhjælp på gård • Medhjælper på forældres gård • Medhjælper på fædrene gård • Opvokset og arbejde på landet • Opvokset og tjente på landet • Passe dyr, høste • Praktisk landbrugsuddannelse • Tjeneste på landet
	• Tjenestekarl på landet • Tjente på en gård • Ungmedhjælper i landbrug • Var på en gård • Ved landbruget • Vindumovergård Gods
9212	• Delvis skovarbejde 6' mand • Skov • Skovarbejde • Skovarbejder

APPENDIX D.2: DISCO-88 koder indenfor uorganisk støv (inorg) eksponering

Koder	• **Udvalgte koder: 20 (inorg), 2 (org + inorg), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Anvendte koder: 12 (inorg), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Ikke anvendte koder:** • **8 (inorg): 7121, 7123, 7133, 8111, 8113, 8151, 8222, 9162** • **2 (org + inorg): 8331, 8332**

DISCO	Spørgeskema tekst
7111	• Stenkulmine
7113	• Stenbrud • Stenhugning • Stenhugger (60er)
7122	• Murer • Murer/murerlærling • Murersvend
7131	• Tagdækker (asfalt) • Arbejdsmand, tagdækker, chauffør
7134	• Arbejdsmand/isolatør • Isolationsarbejde (asbest) • Isolatør • Isolatør stenuld/glasuld • Isolering • Isolering, tagplader • Rockuld ved smelteovne • Rockwool
7211	• Blystøber til akkumulator • Former • Letmetalstøbning – former
7213 + røg	• Alt-mulig-mand hos smed • Arbejdede som 'smededreng' (+ malede med maling og celluloselak) • Arbejdsmand v. vand og gasmester • Automekaniker, pladesmed • Autopladeværksted • Blikkenslager • Blikkenslager, asbest, isolering • Blikkenslager/svejser • Grav og blogsmed • Grovsmed, svejser • Karosseri arbejde – slibning • Kedelsmed • Klejnsmed • Klejnsmed, smed i byggesektor, smed foderstoffabrik • Landbrugsmaskinsmed • Landbrugssmed • Landsbysmed • Maskinarbejder/smed • Metaludstansning på svejsefabrik • Pladesmed • Pladesmed/autolakering • Pladesmed/beholder • Reparationer v landbruget, støv fra vinkelsliber, maskinarbejder, sprøjtemaling af maskiner (tolket som landbrugsmaskinsmed) • Rørlægger • Rørlægger i skibsværft og offshore industri

	• Rørsmed • Sanitet • Smed • Smed – VVS • Smed og svejser • Smed på betonstøberi • Smed/montør • Smed/reparatør cementfabrik • Smed/svejse • Smede og maskinarbejder • Smedearbejde • Smedearbejde (minus svejsning) • Smedearbejde og svejsning • Smedearbejdsmand • Smedelærling • Smedemedhjælper • Smedeværksted • Smedeværksted i røg og os • Smedje • Svejser + kedelsmed • Svejser, smed • Uddannet smed, daglig svejserøg • Vogn og beslagsmed • VVS • VVS blikkenslager • VVS mand • VVS montør
7214 + røg	• Arbejdsmand (værft) • Arbejdsmand i støven på B&W • Skibsbyg arb…. • Skibsbygger • Skibsbygger på værftet • Skibsværft • Slibning af glasfiber • Svejsning inde/ude på skib • Værft

	• Værft arbejde
7215 + røg	• Rigger
7224	• Barberbladefabrik (slibestøv) • Metalsliber • Slibearbejde ved værft • Slibning af biler • Stålborde + slibning • Svejsning, metalslibning • Svejsning/slibning • Værktøjsmager • Værktøjsslibning
8112	• Jernmalm • Molerarbejder • Molerindustri, jord, kloak, beton arb, stenhugning • Stenknuser • Stenknusermaskine • Stenknusning
8121 + røg	• Metal drejer • Metalarbejde • Skrot • Specialarbejder på beholder fabrik (jern) • Stålværkstedsarbejde
8122 + røg	• Blysmeltning • Jernkogeri • Metal smeltning (bly) • Metalsmelter • Smeltet metal • Smeltning af bly
8123 + røg	• Arbejde med og smeltning af bly • Arbejde på jernstøberi • Blystøv • Dania • Former/støber i metal • Håndformer/jernstøberi + metal • Jernstøberi • Jernstøv

	• Jernværk • Kernemager • Lejestøber • Metalstøberi • Renser på metalstøberi • Støber på jernstøberi • Støberi • Støberi – metal • Støberiarbejde • Støbning metal • Svejser + jernstøberi • Svejsning af zink og galvanisering • Svejsning og galvanisering • Svejsning, jernstøberi, metalstøberi • Svejsning, metalstøbning
8131 + røg	• Arbejde på teglværk • Brander teglværk, jord og beton arbejder, landmand • Kedelpasser • Sod fra kedelrensning • Teglværk • Teglværker • Teglværksarbejde • Teglværksarbejder • Udsat for ler og glasstøv som pottemager
8212	• Arbejde med eternit • Arbejder inden for cement industrien • Arbejdet med asbeststøv i perioder • Arbejdsmand eternit/Aalborg Portland • Asbest • Asbeststøv • Asbeststøv, isoleringsstøv • Beton/elementfabrik • Betonarbejder • Betonfabrik

	• Betonindustri • Bådsmand i Aalborg Portland (nok båndsmand…) • Cement • Cement, granit, nedrivning • Cementarbejde • Cementfabrik • Cementformand • Cementindustri • Cementstøber • Cementstøber beton • Cementstøberi • Cementstøv • Cementvarefabrik • Cementvareindustri • Dansk eternitfabrik • Eternit/cement • Eternitarbejder • Eternitstøv (asbest) • Flisefabrik • Flyveaske, støv • Formalet flyveaske • Glasfiber – asbest • Industri – asbest • Kalkværker • Medhjælper cementstøv • Roteroven, cementmølle, Aalborg Portland • Rørdal • Støbearbejder (uspecificeret jern/cement) • Støber (også kodet: betonfabrik)
9311	• Grusgrav
9312 + røg + dampe	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og

	dieselos)
9313	• Altmuligmand v entreprenør • Arbejdsmand, murer, isolatør • Betonfabrik/ murerarbejde • Bygge og anlæg • Byggeri anlæg • Bygningsarbejde • Bygningshåndværker • Entreprenør • Entreprenør (dræning) • Entreprenørarbejde • Entreprenørarbejde/ nedbrydningsarbejde • Gasbetonmontør • Jord og beton • Jord og betonarbejder • Landbrugsentreprenør • Murer (også kodet: tømrer) • Murer og tømrer • Murer/betonarbejder nedrivningsarbejde • Murer/nedrydning • Murerarbejder • Murerarbejdsmand • Murerarbejdsmand, isoleringsarbejder – rockwool og glasuld • Murermedhjælper • Mureroppasser • Murstøv • Nedbryder • Nedbrydningsarbejde, entreprenørarbejde, betonstøv • Nedrivning af lejligheder, murer, mv • Nedrivning og opbygning • Nedrivning/husbyggeri • Ombygning og

	nybygning af boliger mm • Sandblæser • Sandblæsning, cementarbejde, stenknusemaskine • Specialarbejder anlæg og byg
9330	• Havnearbejder • I 25 år – dagligt fejet i lagerhallen hvor jeg arbejdede • Lagerarbejde - betonstøv • Lagerarbejder på Sadolin malerfabrik • Lagermand • Lagermedarbejder

APPENDIX D.3: DISCO-88 koder indenfor røg (fume) eksponering

Koder	• **Udvalgte koder: 3 (fume), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Anvendte koder: 2 (fume), 7 (inorg + fume), 1 (inorg + fume + vapour)** • **Ikke anvendt kode: 1 (fume): 7411**

DISCO	Spørgeskema tekst
5161	• Brandmand
7212	• Akkumulator svejser • Aluminium svejsning • CO2 - svejsning • Elektronik loddearbejde • Fabrik – svejser • Fabrik metalsvejser • Håndlodning • Lodde blykabler • Lodde komponenter som radioarbejde • Loddearbejde • Loddedame • Loddede i flydende loddetin • Loddepige på B&O • Lodning • Lodning (slag) • Lodning af elektronik • Lodning af printplader • Lodning i elektronikindustrien • Lodning på fabrik • Maskinarbejder og svejser • Maskinarbejder/VVS/ isolering/svejsning/ mekaniker (også kodet: landmand) • Maskinoperatør, svejser ved siden af • Metalstøberi/svejsning • Montrice (loddearbejde) • Pressvejsning • Punktsvejsning • Rørsvejsning • Skærebrænding • Skæreolie – svejsning • Smed (svejser) • Svejsearbejde • Svejseos • Svejser • Svejser – acetone • Svejser – metalstøv • Svejser – rørmager • Svejser m. svejsetråd • Svejser og maskinarbejder • Svejser, maskinist • Svejser, skibsbygger • Svejser, skærebrænder • Svejser/mekaniker • Svejser/rørlægger • Svejser/smed • Svejserøg • Svejsning • Svejsning (aluminium), maskinarbejde • Svejsning af rustfrit stål • Svejsning og lign ved reparation af landbrugsmaskiner • Svejsning, fabrik • Tinlodning • TV lodning
7213 + uorg	• Alt-mulig-mand hos smed • Arbejdede som 'smededreng' (+ malede med maling og celluloselak) • Arbejdsmand v. vand og gasmester

	• Automekaniker, pladesmed • Autopladeværksted • Blikkenslager • Blikkenslager, asbest, isolering • Blikkenslager/svejser • Grav og blogsmed • Grovsmed, svejser • Karosseri arbejde – slibning • Kedelsmed • Klejnsmed • Klejnsmed, smed i byggesektor, smed foderstoffabrik • Landbrugsmaskinsmed • Landbrugssmed • Landsbysmed • Maskinarbejder/smed • Metaludstansning på svejsefabrik • Pladesmed • Pladesmed/autolakering • Pladesmed/beholder • Reparationer v landbruget, støv fra vinkelsliber, maskinarbejder, sprøjtemaling af maskiner (tolket som landbrugsmaskinsmed) • Rørlægger • Rørlægger i skibsværft og offshore industri • Rørsmed • Sanitet • Smed • Smed – VVS • Smed og svejser • Smed på betonstøberi • Smed/montør • Smed/reparatør cementfabrik

	• Smed/svejse • Smede og maskinarbejder • Smedearbejde • Smedearbejde (minus svejsning) • Smedearbejde og svejsning • Smedearbejdsmand • Smedelærling • Smedemedhjælper • Smedeværksted • Smedeværksted i røg og os • Smedje • Svejser + kedelsmed • Svejser, smed • Uddannet smed, daglig svejserøg • Vogn og beslagsmed • VVS • VVS blikkenslager • VVS mand • VVS montør
7214 + uorg	• Arbejdsmand (værft) • Arbejdsmand i støven på B&W • Skibsbyg arb…. • Skibsbygger • Skibsbygger på værftet • Skibsværft • Slibning af glasfiber • Svejsning inde/ude på skib • Værft • Værft arbejde
7215 + uorg	• Rigger
8121 + uorg	• Metal drejer • Metalarbejde • Skrot • Specialarbejder på beholder fabrik (jern) • Stålværkstedsarbejde

8122 + uorg	• Blysmeltning • Jernkogeri • Metal smeltning (bly) • Metalsmelter • Smeltet metal • Smeltning af bly
8123 + uorg	• Arbejde med og smeltning af bly • Arbejde på jernstøberi • Blystøv • Dania • Former/støber i metal • Håndformer/jernstøberi + metal • Jernstøberi • Jernstøv • Jernværk • Kernemager • Lejestøber • Metalstøberi • Renser på metalstøberi • Støber på jernstøberi • Støberi • Støberi – metal • Støberiarbejde • Støbning metal • Svejser + jernstøberi • Svejsning af zink og galvanisering • Svejsning og galvanisering • Svejsning, jernstøberi, metalstøberi • Svejsning, metalstøbning
8131 + uorg	• Arbejde på teglværk • Brander teglværk, jord og beton arbejder, landmand

	• Kedelpasser • Sod fra kedelrensning • Teglværk • Teglværker • Teglværksarbejde • Teglværksarbejder • Udsat for ler og glasstøv som pottemager
9312 + uorg + dampe	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og dieselos)

APPENDIX D.4: DISCO-88 koder indenfor damp (vapour) eksponering

Koder	• **Udvalgte koder: 5 (vapour), 1 (inorg + fume + vapour)** • **Anvendte koder: 5 (vapour), 1 (inorg + fume + vapour)**

DISCO	Spørgeskema tekst
1318	• Renseri
7141	• Bygningsmaler • Deltidsmaler • Glasfiber og acetone, maling • Glasfiber/maling • Glasmaler • Gulvlakering • Maler • Malerdampe • Malersvend • Malerværksted • Maling • Maling og stenolie • Skibsmaler • Skibsmaling • Tagmaler
7142	• Autolakerer • Autolakering • Automaler • Billakering • Epoxy • Epoxymaler, borerig, Norge • Hjælpe sprøjtemaler • Industrimaler • Lakerer • Lakering • Maling, epoxy, polyester • Sprøjte og bygningsmaler • Sprøjtekabinemaler, epoxy • Sprøjtemaler • Sprøjtemaler, arbejde med fortynder og triklor • Sprøjteværksted (lak) • Tæppelakering • Undervognsbehandling • Undervognsbehandling af biler • Varm lakering af motorer
8152	• Afrenset metaldele med rensevæske • Bejdsning/afsyring af jern (syrebade) • Dampe – farvninger • Galvanisering • Glasur og begitning af lervarer • Kemisk tøjrensning
8223	• Glasfiberarbejde • Gummifabrik • Industrilakering • Lakering af mobiler • Lakering fabrik • Lystryk (ammoniak-dampe) • Polyester/glasfiber • Rensning af genbrugsgiftflasker • Reparationsarbejde/ limning af glasfiber • Vulkanisør
9312 +uorg +røg	• Asfaltarbejde • Asfaltfabrik • Fræsning af asfalt • Paming/maling, asfaltarbejde • Vejarbejde • Vejmand (benzin og • dieselos)

APPENDIX E. PAPER I

Occupational chronic obstructive pulmonary disease in a Danish population-based study

Else Toft Würtz, Vivi Schlünssen, Tine Halsen Malling, Jens Georg Hansen, Øyvind Omland

COPD. 2014 Nov 21. [Epub ahead of print]

APPENDIX F. PAPER II

Occupational chronic obstructive pulmonary disease among Danish women: a population-based cross-sectional study

Else Toft Würtz, Vivi Schlünssen, Tine Halsen Malling, Jens Georg Hansen, Øyvind Omland

Submitted

APPENDIX G. PAPER III

Occupational COPD among Danish never smokers – a population-based study

Else Toft Würtz, Vivi Schlünssen, Tine Halsen Malling, Jens Georg Hansen, Øyvind Omland

Occup Environ Med, 2015, 72, 456-9.

APPENDIX H. PAPER IV

Occupational exposure increases the four-year incidence of COPD among 45-84-year old Danes

Else Toft Würtz, Vivi Schlünssen, Tine Halsen Malling, Charlotte Brasch-Andersen, Jens Georg Hansen, Øyvind Omland

Submitted

SUMMARY

Chronic Obstructive Pulmonary Disease (COPD) is a common disease. The main risk factor is smoking although 15% of the COPD cases are expected to be preventable if the occupational exposures from vapour, gas, dust, and fume were eliminated; the population attributable fraction (PAF).

The thesis addresses the association between occupational exposure and COPD in a population-based cohort of Danes aged 45-84-years.

4717 participants were included at baseline and 2624 at the four year follow-up. COPD was defined by spirometry and the occupational exposure was based on specialist defined jobs and questionnaires. The main occupational exposure was organic dust and 49% reported no lifetime occupational exposure.

The results suggest occupational exposures to be associated to COPD also in never smokers and women. We found an exposure-response relation in the cross sectional analyses. The results are in accordance with other international studies. The estimated PAFs were high among never smokers, while no comparable PAF previously have been established among women. The analyses indicate an association between occupational exposure and incident COPD.

Recognising that exposures from work over time might have an impact on the development of COPD ought to be transformed to preventive efforts to eliminate occupational COPD and improve public health.

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